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Overweight in the Aged

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OBESITY has been implicated as a health hazard in many studies. It is almost universally accepted as important in permitting the expression of diabetes mellitus, frequently assumed to be a causal factor in atherosclerosis, and an aggravating factor in various forms of arthritis, hypertension, and other diseases. The idea that obesity is a health hazard gained major support from studies by Dublin and Marks[1] on the mortality experience of insurance companies with overweight individuals. These writers reported an aggregate mortality of 150 per cent in overweight people as compared with policy holders of average weight for height.

Keys[2] has criticized these studies as failing to separate those over average weight with increased body fat from those with increased non-fat tissue and has questioned whether the insured overweight group is representative of the overweight population.

Armstrong *et al.*[3] have reported that 7 per cent of the population from age 25 through 59 years is 20 per cent or more heavier than the average weight for their height. The average weight for height tables on which these studies are based show a gradual increase in weight for men and women from 25 to 59 years of age.

The implication of these data and the lack of information on average weight in older persons prompted this study of body weight on some 700 people over age 65.

MATERIAL AND METHODS

The subjects studied attended either an outpatient clinic or were residents in domiciliary institutions for elderly people in Virginia. Less than 10 per cent were Negroes. All subjects were ambulatory and those with debilitating chronic disease or recent acute changes in weight were eliminated from the study. Each subject's height and weight, with shoes and ordinary indoor clothing on, were measured. A careful weight history was recorded. The weight history included attempts to get known maximum and minimum weights and to date these by the age at which the patient finished school, married, entered military service or experienced other important personal events. This information checked against the few available records seemed reasonably accurate for the group included in this report.

Data on 681 people, 474 males and 207 females, were sufficiently complete to permit analysis.

RESULTS

Since the number of subjects in this study is relatively small, the weights are given by decades for each two inches of height. The data on average weight for males are given in Table

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TABLE I

Average Weight for 474 Males by Decades and Heights (Number of Subjects in Each Group is in Parentheses Beside Each Average Weight)

Heights in Inches	Weights According to Age Periods		
	65-74	75-84	85-94
54-58	167 (4)	138 (2)	
59-60	119 (4)	200 (1)	
61-62	135 (28)	134 (7)	
63-64	143 (36)	146 (10)	136 (6)
65-66	152 (90)	151 (35)	140 (8)
67-68	161 (101)	153 (31)	153 (8)
69-70	165 (60)	163 (14)	167 (5)
71-72	180 (21)	149 (4)	153 (2)
73-74	139 (3)	173 (2)	
75-76	217 (1)		

TABLE II

Average Weight for 207 Females by Decades and Heights (Number of Subjects in Each Group Given in Parentheses Beside Each Average Weight)

Heights in Inches	Weights According to Age Periods		
	65-74	75-84	85-94
54-58	126 (5)	115 (8)	99 (5)
59-60	136 (15)	127 (29)	127 (9)
61-62	132 (27)	127 (26)	121 (9)
63-64	143 (17)	137 (28)	127 (7)
65-66	146 (11)	134 (9)	131 (4)
67-68	157 (2)	170 (1)	-
69-70	-	-	-

I and that for females in Table II.

The weight trends with increasing age for the more common heights are illustrated in Figure 1. The average weights for the ages 25 to 59 were taken from the average weight tables furnished by the Metropolitan Life Insurance Company. In these tables the increase in weight with each inch of height is rather constant within the range of several inches from age 25 to 59, so the weights in Figure 1 are average weights for each two inches of height.

The degree by which those overweight exceeded the average calculated for age and height in this study is given for males in Table III and for females in Table IV. Weight histories on this group indicate that 48.4 per cent of the females and 21.1 per cent of the males reached this overweight category after age 60. For those within 20 per cent of the average weight at the time of study, it appeared by history that 30.9 per cent of females and 25.5 per cent of the males had been 20 per cent or more above average weight at some period in their lives. Tables V and VI give the percentage by which those formerly 20 per cent or more overweight exceeded the average for the age at which their weights were highest.

Since from Figure 1 maximum average weight appears to occur around 55 to 59 years, the percentage of subjects who were greater than 20 per cent of this weight was determined; 10.9 per cent of males and 8.2 per cent of fe-

TABLE III

Percentage of Males Who Were 20 Per Cent or More Above Average Weight by Decades

Degree of Overweight	All Ages N=474		Age 65-74 N=339		Age 75-84 N=105		Age 85-94 N=30	
20%+	20	38.5%	12	32.4%	7	50.0%	1	
30%+	21	40.4%	16	43.3%	5	35.8%		
40%+	6	11.5%	5	13.5%	1	7.1%		
50%+	5	9.6%	4	10.8%	1	7.1%		
Total 20% or more above average weight	52	10.9%	37	10.9%	14	13.3%	1	3.3%

TABLE IV

Percentage of Females Who Were 20 Per Cent or More Above Average Weight by Decades

Degree of Overweight	All Ages N=207		Age 65-74 N=76		Age 75-84 N=99		Age 85-94 N=32	
20%+	13	39.4%	3	25.0%	9	56.3%	1	20.0%
30%+	12	36.4%	5	41.7%	5	31.3%	2	40.0%
40%+	8	24.2%	4	33.3%	2	12.5%	2	40.0%
50%+	-	-	-	-	-	-	-	-
Total 20% or more above average weight	33	15.9%	12	15.7%	16	16.1%	5	15.6%

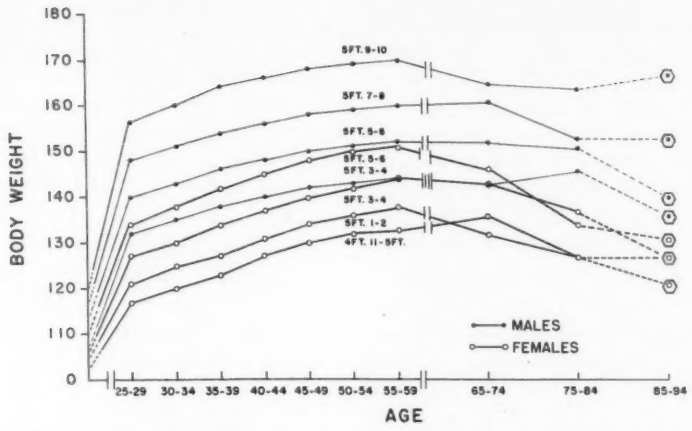

Fig. 1. Average weights for age for males and females. Average weights from 25 to 59 years compiled from the average weight tables of the Metropolitan Life Insurance Company. Average weights for the 65- to 94-year group compiled from the group studied. Weights given for age 85 to 94 are the averages from less than ten subjects.

males were 20 per cent or more heavier than the average weight of the 55 to 59-year group in the standard weight tables.

DISCUSSION

The number of subjects included in this study is too small to permit great accuracy in establishing average weight for older people. However, the data are probably adequate to indicate certain trends. The weight curves in Figure 1 suggest that the gradual increase in average weight which occurs from age 25 to 59 has stopped by the 65-to-74 decade and that average weight tends to plateau during that period. After that decade the evidence appears to be that average weight tends to decline and is roughly that of the average of the weights at age 25 to 29, for both men and women during the 85 to 94 decade.

The finding that 30.9 per cent of females and 25.5 per cent of males, who were within 20 per cent of the average weight at the time of the study, had been overweight at some period in their lives is surprising. The accuracy of retrospective studies of this type are always in doubt; however, allowing for a very large error, this information would suggest that the group surviving to old age contains a large number of people who have been overweight.

Mortality studies[1] of overweight people who reduced their weights to within the limit acceptable for standard insurance show that weight

TABLE V

Incidence and Degree of Excessive Weight in Males Who Were Within 20 Per Cent of the Average Weight at the Time of the Study but Who Had at Sometime Exceeded the Average Weight by 20 Per Cent or More

Degree of Overweight	All Ages N=474		Age 65-74 N=339		Age 75-84 N=105		Age 85-94 N=30	
20%+	41	33.9%	27	38.1%	9	25.7%	5	33.3%
30%+	48	39.7%	30	42.2%	13	37.1%	5	33.3%
40%+	20	16.5%	6	8.5%	9	25.7%	5	33.3%
50%+	12	9.9%	8	11.2%	4	11.5%	-	-
Total Formerly 20% or more above average weight	121	25.3%	71	20.9%	35	33.3%	15	50.0%

TABLE VI

Incidence and Degree of Excessive Weight in Females Who Were Within 20 Per Cent of the Average Weight at the Time of the Study but Who Had at Sometime Exceeded the Average Weight by 20 Per Cent or More

Degree of Overweight	All Ages N=207		Age 65-74 N=76		Age 75-84 N=99		Age 85-94 N=32	
20%+	15	23.4%	3	13.1%	5	18.5%	7	50.0%
30%+	29	45.3%	12	52.1%	13	48.1%	4	28.6%
40%+	8	12.5%	2	8.8%	5	18.5%	1	7.1%
50%+	12	18.8%	6	26.0%	4	14.9%	2	14.3%
Total Formerly 20% or more above average weight	64	30.9%	23	30.2%	27	27.2%	14	43.7%

reduction results in significant improvement in mortality for this group. Few in the group studied here reported any serious attempts at weight reduction. For the most part, weight reduction in the group of former overweights appeared to be the result of natural or unplanned variations in weight. Certainly it would seem that the incidence of excessive weight would be much higher if calculated on highest lifetime weight rather than the incidence of excessive weight at one time in any segment of the population. Little is known of the effects of major weight shifts over a period of years. Pomeranze[5] has suggested that the "wear and tear" of repeated major shifts in weight may result in "failure of a predisposed organ."

The number of people who were 20 per cent or greater than the average weight for age at the time of the study given in Tables III and IV is higher than the 7 per cent in the general population. However, historically, it appears that 21 per cent of the males and 48 per cent of females in this group reached a weight of 20 per cent or more over the average after age 60. This might be the result of weight gain for some individuals or the result of the declining average with age. The number of males with weights 20 per cent or more above average was the same, 10.9 per cent vs. 10.9 per cent, whether the calculated averages for the older ages or the averages of the 55- to 59-year period were used. Analysis of the individual cases showed that only five individuals shifted groups when the two different averages were used as standards for comparison. Only 8.2 per cent of the females were 20 per cent or more above the average weight for 55 to 59 years, while 15.9 per cent were this much above the average calculated for the older age group. The changes in this group were largely due to maintenance of a weight which became 20 per cent or more above the average as the average decreased fairly sharply with advancing age. This change in average weight is illustrated in Figure 1. These studies indicate that the percentage of people who are 20 per cent or more overweight after age 65 is at least equal to that of overweight people in the general population. One would not expect to find this many overweight people over 65, using the mortality experience of insurance companies with overweight people as a guide.

Average body weight seems to plateau at the 65 to 74 decade, being roughly that of the 55- to 59-year group. After the 65 to 74 decade, the average weight decreases and the decrease is more abrupt for females than for males. Historically, many of the people who are within 20 per cent of the average weight for age after age 65 were at some time 20 per cent or more above the average weight for age. As far as obesity is concerned, the implication of these studies is that the incidence of obesity in older people is as great or greater than the younger people. Keys[4] has demonstrated that inactive people are fatter than more active people of the same weight. Certainly, the subjects of this study were relatively inactive and it seems reasonable to assume that those who were overweight would have a higher body fat content than a younger and more vigorous group with the same average weights.

SUMMARY

A study of body weight on some 700 people over age 65 revealed that 11.0 per cent of males and 15.9 per cent of females were 20 per cent or more above the average weight for their heights and age. Of subjects 65 years or older 10.9 per cent of males and 8.2 per cent of females were 20 per cent or more heavier than the average weight of the 55- to 59-year-old group as presented in the average weight tables used by insurance companies. The percentage of people who are 20 per cent or more above average weight after age 65 is at least equal to that of the general population. Average weight for people in this older group tended to plateau at the 65- to 74-decade and fall thereafter. Weight histories indicated that for those within 20 per cent of average weight at the time of study, 30.9 per cent of the females and 25.5 per cent of the males had at some period exceeded the average weight by 20 per cent or more.

The data suggest that the incidence of obesity is as great or greater than among younger adults.

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A Study of Methods Used in a Reducing Program for Excessively Overweight Women

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LIFE insurance statistics and clinical studies have demonstrated that obesity is one of the chief threats to longevity and to continued good health in later years.[1]

The need for weight control programs is evident.[2] The literature contains many reports dealing with various attempts at weight reduction and maintenance. For example, Williams *et al.*,[3] in a study on overweight nurses, used diets of 400 to 1200 calories and administered anorexigenic compounds of the amphetamine type. They concluded that there are no "magic" drugs that can satisfactorily bring about weight loss in the face of continued ingestion of excessive amounts of food. Sapoznik,[4] by treating patients suffering from different degrees of hypertension with several anorexigenic drugs, concluded that Obolip° was the most effective. (This product consists of a mixture of certain lipotropic factors, amphetamine, phenobarbital, and methyl cellulose.) He was able to cause a considerable weight loss during a period of six weeks. Mayer[5] has shown that an increased energy output was effective in controlling weight gains in animal experiments, and he postulated that exercise would be effective in human weight reduction.

In view of these typical reports, a study was designed to evaluate several existing methods of treatment as practiced by the medical profession, public health personnel, and nutritionists. Since it was not feasible to confine the subjects in this study to a hospital or to provide a controlled feeding program, they were asked to cooperate in a project in which a suggested meal pattern was provided. The success of such a plan would depend on educational procedures which could develop in the subjects an awareness of sound nutritional principles.

MATERIAL AND METHODS

Subjects for the study were selected by the staff of the Woman's College Hospital. All were women and most of them were patients referred to this project by their private physicians. The majority were in the middle-income bracket and had some high-school education. Some held office positions; others looked after their families at home. All were extremely overweight. Preliminary extensive histories and medical examinations were made to rule out complicating disease, such as endocrine disorders. The laboratory tests[6,7] which were done at the commencement of the program and again after a six-month interval included the following: basal metabolic rate; fasting blood sugar; liver-function tests (thymol turbidity, mercuric chloride, cephalin-cholesterol flocculation), serum proteins, total serum cholesterol, hemoglobin, and routine urinalysis. To help us understand more fully the special problems and home situation of each person, we visited the subjects to obtain a personal history

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TABLE I
Plan of Medication

Period	Group I	Group II	Group III	Group IV
1	Obolip[a]	—	Placebo	—
2	Obolip	—	Placebo	—
3	Lipocap[b] and B_{12}[c]	Lipocap and B_{12}	Lipocap and B_{12}	—
4	Obolip	—	Obolip	—

[a] Obolip: phenobarbital, 16 mg; *d*-amphetamine sulfate, 5 mg; choline bitartrate, 400 mg; *dl*-methionine, 150 mg; vitamin B_{12} 4 μg; methyl cellulose, 160 mg.
[b] Lipocap: choline bitartrate, 450 mg; *dl*-methionine, 150 mg; inositol, 100 mg.
[c] Vitamin B_{12} (4 μg) supplied by Merck & Co., Montreal, Quebec.

in order to supplement the information previously recorded. The subjects kept a one-week dietary record, for which the approximate nutritive value was calculated for comparison with the Canadian Dietary Standards.

Procedures followed throughout the program included dietary education and evaluation, routine medical supervision, and, where advisable, instruction in physical exercise.

In January, 1956, 24 women, ranging in weight from 148 to 300 pounds and in age from 15 to 61 years, were divided in two equal groups (I and II), and enrolled in a six months' program. The study was divided into four periods of six weeks each, during which all subjects, in addition to nutritional education, received medication as indicated in Table I. In October, 1956, two more groups of 12 women each, III and IV, were started. These subjects varied from 25 to 60 years in age and from 179 to 254 pounds in weight. The plan for medication for these two groups is indicated in Table I. All weight losses were recorded weekly.* Data were tabulated at the end of each six-week period.

As the program proceeded, some of the subjects dropped out of their own accord. Of the 48 members, 4 moved away from the city, 2 became pregnant, 2 developed chronic illnesses, and 15 lost interest. Of those who lost interest, one-third showed lack of cooperation and irregular attendance before the third week. As a result, there were only 8, 5, 6, and 6, who finished the study in groups I, II, III, and IV, respectively. It is significant that the combination of a medical recommendation to lose weight plus a planned educational program failed to maintain interest and cooperation in about one-third of the subjects.[8]

* Neohydrin (Lakeside Laboratories), an oral mercurial diuretic, was prescribed for some of the subjects who showed edema.

TABLE II
A Comparison of Methods to Determine Ideal Weight in Obesity Using Four Different Procedures

	Group			
	I	II	III	IV
Number of subjects	8	5	6	6
Average age (yr)	28.5	51	35	42
Average height (in.)	65.4	63.0	63.7	65.0
Average weight (lb)	247	188	230	210
Ideal weight (lb) as determined by:				
Lean body mass[12]	131	126	127	130
Wrist measurement	135	123	132	132
Life insurance tables[10]	141	128	132	135
Nomograph[11]	145	135	137	143

Groups I and II were continued for a second series of four six-week periods, using the same medication as in the first series.

At the beginning of the study it was explained that the 1,100 to 1,200 calorie pattern to be followed by the group was designed to supply all the food nutrients in amounts recommended for good health. The dietary plan supplied approximately 75 to 80 g of protein, 130 g of carbohydrate, and 30 g of fat. Each subject kept a daily food intake record which was checked each week. The women were taught to plan menus which fitted into their family pattern but met their own dietary requirements. In some cases, it was necessary to assist them with their weeklp shopping lists. The educational procedures included formal lectures and demonstrations, group discussions, and individual consultation. There was no

attempt at coercion during any phase of the program.

When the height and weight of each person had been determined, the daily caloric requirement was estimated by means of the Boothby and Berkson Food Nomogram.[9,11] The type of frame was determined by means of the wrist measurement and from this, the ideal weight for each person was estimated.* Ideal weights were also obtained from the standard height-weight tables[10] and the per cent above ideal weight was determined on a nomograph.[11] Overweight was also calculated in percentages above the lean body mass[12] which was taken as a standard of 2 pounds per inch of height. The expected loss of weight and the actual weight loss for each subject was charted on a graph for purposes of comparison. The ideal weights for those subjects who participated throughout the project were calculated from the height, weight, and wrist measurement using four different methods. Data are presented in Table II. It is apparent that the four methods give reasonably comparable results. The differences would not appear to be significant in terms of substantially altering the estimated caloric requirements. The discrepancy in average weight between groups I and II became more apparent after some members ceased to participate. As the project progressed, several of the lighter members of group I and some of the heavier members of group II lost interest. The same factors affected the average weights of the remaining subjects in groups III and IV.

Each week supervised exercise was available and those participating were instructed in a course of prescribed exercises, to be done at home each day. The women were encouraged to increase their general activity and to take part in sports when possible.

* Measurements and calculations are as follows:

	Type of frame acc. to wrist measurement	
	Small-boned	Large-boned
Height		
Under 5′3″	5½″ or under	Over 5¾″
5′3″–5′4″	6″ or under	Over 6½″
Over 5′4″	6½″ or under	Over 6½″
Ideal weight	100 lb for 5′ ht plus 5 lb for each addl. inch	110 lb for 5′ ht plus 5 lb for each addl. inch

RESULTS AND DISCUSSION

From the personal history of these subjects it is apparent that 41 of the 48 (85 per cent) had been inclined to overweight since childhood. The remaining 7 attributed their excess weight gain to long recuperative periods following operative procedures or chronic illnesses. Pregnancy seemed to be the most important factor adding to an already obese condition. Many of the women had experience with various kinds of reducing programs, all of which ended in failure. From a study of the dietary records which the subjects kept before the commencement of the project, it was apparent that there was a lack of meal planning, resulting in an inadequate intake of proteins, vitamins, and minerals. In no case did they partake of an adequate breakfast. In some instances, the daily caloric intake was well below 1,200 calories. Since this record was made the week prior to the onset of the project, the subjects may have curtailed their food consumption. As other studies of obese people[13] have indicated, however, they are frequently inaccurate in recording food intake.

It became evident from comments that the subjects thought they were eating more when following this dietary pattern then when they had been maintaining or gaining weight. Possibly essential foods providing 1,200 calories have greater satiety value than greater quantities of the less essential foods. Probably due to liberal measurement of food, the actual caloric intake of many of the subjects may have exceeded 1,200 calories.

The results of the laboratory tests showed that the basal metabolic rate of the subjects varied from −13 (87 per cent) to +17 (117 per cent). The fasting blood sugar was in a range of 79 to 112 mg per 100 ml. Three arbitrary liver-function tests were used and showed the greatest variation of any of the laboratory determinations, with abnormal levels in two-thirds of the subjects. The individual ranges were 0.25 to 7.25 units in the thymol turbidity, 0 to 90 units for mercuric chloride, and 0 to 4 plus

TABLE III
Weight Loss Record for Series I

Subject	Age	Initial weight (lb)	% above ideal weight	Weight loss (lb)					% of required loss	
				Per. 1	Per. 2	Per. 3	Per. 4	Total	Per. 1–4[b]	Per. 1–2[c]
Group I										
O.P.	17	215	59.3	18	5.5	1	−0.5[a]	24	30.0	29.1
G.G.	22	268	123.3	13	10	2	5	30	20.3	15.5
B.N.	25	208	48.6	18	9.5	0.5	5	33	48.5	40.4
P.S.	28	271	86.9	4	10	5	2	21	16.7	11.1
S.S.	29	236	62.8	15	6.5	−5.5	3	19	20.9	23.6
C.P.	30	226	73.8	14	3	1	2.5	20.5	21.4	17.7
D.C.	32	272	117.6	28	20.5	2	1.5	52	35.4	33.0
L.K.	45	278	105.9	8	3	0	3	14	9.8	7.7
Group II										
E.G.	43	176	30.4	14.5	6.5	9	2.5	32.5	79.3	51.2
F.M.	47	148	34.5	12	3	2	2	19	50.0	39.5
H.R.	51	182	51.7	8	0	2	−2	8	12.9	12.9
D.G.	53	211	75.8	10	−1	3	2	14	15.4	9.9
R.M.	61	220	63.0	12	5	4.5	1.5	23	27.1	20.0
Group III										
C.G.	25	204	56.9	14	8	10	0	32	43.2	29.7
L.B.	33	251	100.8	10.5	8.5	4	−2	21	16.7	15.1
V.B.	33	204	56.9	13	4	7	6	30	40.5	23.0
M.M.	34	230	91.7	12	−3.5	0.5	0	9	8.2	7.7
E.G.	37	240	84.6	10	1.5	4.5	0	16	14.5	10.5
M.B.	49	254	88.1	11	1	−9	2	5	4.2	10.1
Group IV										
B.B.	27	196	50.8	7	7	−1	−0.5	12.5	18.9	21.2
A.P.	32	179	49.2	4.5	2.5	−1	1.5	7.5	12.7	11.9
J.C.	36	208	43.4	9	8	1	5	23.0	36.5	27.0
H.M.	42	207	47.9	12.5	−2.5	2	4.5	16.5	24.6	14.9
F.R.	56	246	89.2	16	21	8	7	52	44.8	31.9
J.A.	60	221	70.0	5	5	2	0	12	13.2	11.0

[a] A negative value indicates a gain in weight.

[b] $\frac{\text{Total loss (lb)}}{\text{Loss required (lb)}} \times 100.$

[c] $\frac{\text{Loss for periods 1 \& 2 (lb)}}{\text{loss required (lb)}} \times 100.$

in the cephalin-cholesterol flocculation tests. The total serum proteins were essentially normal in all but two subjects, whose levels were low—4.8 and 5.5 g per 100 ml. Total serum cholesterol values varied from 174 to 293 mg per 100 ml., and exhibited the expected inverse relationship to the individual basal metabolic rates.

There was an increase in the pulse rate and blood pressure in 80 per cent of the women after two weeks' therapy with Obolip. The blood pressure rise was more marked in those subjects who had some elevation before starting the capsules. No significant change in pulse or blood pressure was found when another lipotropic preparation (Lipocaps), containing no amphetamine, was used. The hemoglobin level dropped in the less cooperative subjects who were not adhering to the diet. The routine urinalysis did not show any change with medication or diet.

The weight loss data for Series I are presented in Table III. None of the subjects attained their calculated ideal weight. Those subjects with the least amount of excess weight had the greatest degree of success. When weight reduction is expressed as percentage of the required weight loss, groups I, II, III, and IV lost an average of 25.5, 37, 21, and 25 per cent, respectively.

TABLE IV
Weight Loss Record for Series I and II

Subject	Initial weight (lb)	Loss (lb) in Series I	Loss (lb) in summer vacation	Loss (lb) in Series II					Net loss (lb)
				Period 1	Period 2	Period 3	Period 4	Total	
Group I									
O.P.	215	24	−10.5[a]	1	−4.5	−3.5	−1.5	− 8.5	5
G.G.	268	30	−9	−4	−8	−6	4	−14	7
B.N.	208	33	−1	0	6	−1.5	−0.5	4	36
P.S.	271	21	3	1	4.5	−1.5	0	4	28
S.S.	236	19	−5	−5	2	−3	4	−2	12
C.P.	226	20.5	−2	−2.5	0	4	−6	−4.5	14
D.C.	272	52	−3	7	−1.5	−7.5	8	6	55
L.K.	278	14	6	−3	−1	2	−4	−6	14
Group II									
E.G.	176	32.5	3.5	1.5	−1.5	1	1	2	38
F.M.	148	19	−1	1	0.5	−1.5	1	1	19
H.R.	182	8	0	−2	2	−5	0	−5	3
D.G.	211	14	−2	2.5	−3.5	5.5	−1.5	3	15
R.M.	220	23	−4.5	−2	−0.5	−2	2	−2.5	16

[a] A negative value indicates a gain in weight.

Eighty-one per cent of all weight lost by all subjects in Series I was lost in periods 1 and 2 (twelve weeks). When the weight loss is considered for each group, it is seen that in the first twelve weeks groups I, II, III, and IV lost respectively 87, 72.5, 80, and 77 yer cent of all the weight that was lost in Series I. Enthusiasm, a factor common to all groups in the early stages of the program, contributed to the large initial weight loss.

As has been said, 87 per cent of the total weight lost by the subjects in group I was lost in the first two periods. This percentage is greater for this group than for any other group, possibly due to the effect of the anorexigenic drug, Obolip. It will be noted from the data that there was a decreased weight loss in the second six-week period. In the same period, the subjects frequently commented that the effectiveness of the appetite inhibitor seemed to be decreasing. The observation concerning the short-term efficiency of appetite inhibitors has been made by Williams[3] and Sapoznik.[4] In the third period, groups I, II, and III received Lipocaps and vitamin B_{12}. The losses attained were insignificant, and the medication appeared to be ineffective in stimulating weight loss. Group IV, which received no medication in this period, also had insignificant losses. During the fourth period, group I had an increased weight loss almost three times that of the previous period. This may be related to the renewed physical and psychologic effect of Obolip. Group III received Obolip for the first time in period 4. For this group, the medication seemed to be ineffective, indicating that the appetite inhibitor may be more effective when introduced in early stages of treatment. Groups II and IV, receiving placebos and no medication, respectively, had insignificant losses during this period. Two of the subjects, D. C. and F. R., lost a substantial amount of weight—52 pounds—but they were not successful in losing the remainder necessary to attain ideal weight.

During the summer months, members of groups I and II were encouraged to continue their weekly visits to the clinic, but vacations and week-end trips disturbed their dietary regimen. In September, 1956, these two groups were reassembled and the same experimental plan was repeated. The data regarding their weight losses in the second series are presented in Table IV. The large weight losses experienced at the beginning of the experiment were not attained by any member of group I or II. Only six members lost an additional amount. The other subjects gained significant amounts to substantially reduce their net loss for the two series.

The effect of the physical education program was difficult to assess because the program was limited. Due to excess overweight of the subjects and the resulting inactivity, muscular stiffness was a great deterrent to continuous participation. The difficulty in obtaining clothing suitable for such exercise was another factor which made the subjects less enthusiastic. Again, there was no coercion used in this aspect of the program.

From these studies, it appears that subjects who are moderately overweight are more likely to be successful in attaining a more normal weight than those who are excessively overweight. When the history of the past several years was checked for each subject, a pattern of 10 to 20 pounds weight gain per year was typical. During the course of the experiment, each subject in groups I and II ended the second series with a net loss, which indicates that their gaining pattern was arrested.

When subjects are only 10–25 per cent overweight, a program such as described here would be satisfactory because the initial weight losses are sufficient to bring the subjects near the so-called ideal weight within a period of less than three months. When subjects need to lose up to 100 pounds, the factors which have been considered here are not adequate for such a great weight loss, because of an apparent inability to permanently change long-established eating habits. From these observations, it becomes readily apparent that the need for preventive education during childhood, adolescence, and pregnancy is great.

SUMMARY

Forty-eight women were enrolled in a weight-reduction program of six months' duration. Of these, 25 attended regularly. These 25 women ranged in age from 17 to 61 years, and their initial weight varied from 148 to 278 pounds. The subjects were divided into four groups for ease of dietary education and evaluation of medical treatments. Two of these groups were followed for a second series of six months. Eighty-five per cent of the 48 subjects initially enrolled in the program had had a tendency to be overweight since childhood.

Seventy-nine per cent of the total weight loss of all subjects in Series I occurred in the first twelve weeks. Obolip may have been an effective adjunct in the early stage of the program but none of the subjects attained her estimated ideal weight during the study.

A dietary survey carried out prior to the commencement of the program revealed that the subjects had a very limited knowledge of meal planning or sound nutritional principles. Even after an intensive educational program, there seemed to be an inability on the part of many of the subjects to continue such a dietary regimen over a prolonged period. This was a contributing factor in the unsuccessful attempts of the majority to attain their ideal weight.

A weight-reduction program for individuals under normal living conditions was found to be only partially successful. The need for good nutrition education for the prevention of overweight is indicated.

ACKNOWLEDGMENT

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From the day on which she weighs 140, the chief excitement of a woman's life consists of spotting women who are fatter than she is.—HELEN ROWLAND

The Effects of Exercise on Blood Cholesterol in Middle-aged Men

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RECENT research suggests a relationship between high blood cholesterol and early onset of atherosclerosis.[1–5] The specific factors which control blood serum concentrations of cholesterol have been reviewed elsewhere.[2,4,6] Most of the investigations to date have been in the area of dietary control. This approach appears promising, but limitations are already evident. Apparently there has been little study of the role of physical exercise in the regulation of blood cholesterol concentrations.

REVIEW OF PREVIOUS STUDIES

Chailley-Bert and co-workers[7] studied the concentrations of blood cholesterol immediately before and after exercise. An increase in blood cholesterol following exercise was observed for 5 subjects and no change in blood cholesterol with exercise for 1 subject. The authors concluded that the increased concentration of cholesterol in blood serum following exercise may have been associated with the first steps in the metabolism of cholesterol. Evidence that cholesterol is eliminated by the skin and the lungs was discussed. The conclusion was drawn that exercise may increase cholesterol metabolism by stimulating endocrine gland activity, hence increasing perspiration and respiration. Thus there may be an eventual lowering of the pre-exercise cholesterol level.

The authors also compared 10 sedentary subjects in middle age with 7 active subjects of approximately the same age. The active group had lower blood serum cholesterol values. The difference between the two groups was quite large. Although no statistical analysis was made, it appeared that the difference would be significant. In another part of the study, three sedentary middle-aged workers (two females and one male), whose blood cholesterol was reasonably high, were placed on a conditioning program consisting of daily 5 km walks and exercises involving rapid and deep respiration or cycling. After the conditioning program, the blood cholesterols were appreciably lower in all three subjects. The period of conditioning was six months in one case, two months in the second, and four months in the third case.

Mann[8] reported the results of a study of 3 subjects. Doubling the calorie supply had no effect on serum lipids as long as the excess of energy was dissipated through exercise. When exercise was restricted and fat deposition occurred, the serum cholesterol concentrations were doubled. Weight reduction by food restriction promptly returned the serum elevations to their original values. Both of these studies, although limited, indicate that a pro-

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gram of exercise tends to lower blood cholesterol values.

On the other hand, Keys and co-workers[3] failed to find that physical activity per se was related to differences in blood serum cholesterol of various population groups. They also found no effect of exercise on blood cholesterol in nine young men who were in caloric balance.[9]

Animal work points to a reduction of total blood cholesterol with exercise. Although Wong, Simmons, and Hawthorne[10] observed no reduction in blood cholesterol when cholesterol-fed chicks were exercised, the experiment was complicated by the administration of testosterone propionate to the cockerels. In a later experiment[11] when androgen treatment was omitted, exercise was effective in reducing blood cholesterol levels of chicks on a high cholesterol diet. Brown and co-workers[12] also reported a reduction in serum cholesterol by exercising cholesterol-fed rabbits daily.

PROCEDURE

The subjects were 31 adult males who were members of the Michigan State University faculty. They were divided into a control group and an exercise group. The control group was composed of 15 subjects who followed their customary routine of activity throughout the experiment. There were 16 men in the exercise group. These subjects were given supervised exercise for a period of three months. Four of the exercise subjects continued participation for a period of six months. For statistical calculations, these 4 subjects (hereafter referred to as the select group) are also included in the general exercise group.

A sample of venous blood was taken from the antecubital vein in the early morning when the subject was in a postabsorptive state. This was repeated twice more at weekly intervals at the beginning and again at the end of the experiment. Serum was separated from the cells by centrifugation.

Free and total cholesterol were determined by the procedure of Schoenheimer and Sperry[13] as modified by Sperry[14] and Foldes and Wilson.[15] The initial total blood serum cholesterol for each subject was compared with the mean values for men of similar age according to the frequency distribution reported by Keys.[16] If the serum cholesterol for an individual subject was greater than the mean plus one standard deviation for men of comparable age, the subject was considered to have a "high" blood serum cholesterol. Five of the 31 subjects were judged in this manner to have elevated blood serum cholesterol concentrations.

It was possible to record resting electrocardiograms before and after the three-month experimental period on eight of the exercise and seven control subjects. All records were obtained on a Model 77, four-channel Sanborn direct-writing recorder by the same operator. Three leads were taken simultaneously in the following order: three standard leads; three aV leads; V_1, V_2, and V_3; and finally V_4, V_5, and V_6. Respiration was recorded on the fourth channel throughout. All records were studied by a cardiologist* and individual written reports for each record of each individual were made by him. These analyses included P-R, QRS, axis deviation, rhythm, and Bazzet's index, plus a general interpretation.

In addition, a statistical analysis was made of the following measurements: pulse rate, P-R interval, QRS duration, Q-T interval, QRS and T frontal-plane vectors (amplitude and direction), amplitude and direction of frontal-plane ventricular gradients and angle between the spacial QRS and T vectors. The latter employed the method of Langner.[17]

All electrocardiogram measurements were made according to the recommendations of the original Committee of the American Heart Association and the Cardiac Society of Great Britain and Ireland and the most recent report of the Committee of the American Heart Association for the standardization of precordial leads.

Each subject in the experiment was given a medical examination by a physician† of the University Health Service before being assigned to either the exercise or control group. If assigned to the control group, the subject was

* We are indebted to Dr. Robert Stow for this part of the work.

† Acknowledgment is made to Dr. Robert N. Monfort of the University Health Service for examining the subjects.

asked to continue his activities as before, and, in every instance, this was a rather sedentary life with no moderate or vigorous exercise taken regularly.

This was based upon the results of the written questionnaire filled in by the subjects. Some of the subjects reported that they took considerable exercise during the summer months but during the rest of the year except for occasionally shoveling snow, no appreciable physical exercise was taken around the home on weekends or after working hours. Some of the subjects had hobbies but none of these involved vigorous physical activity. With one exception, the men all rode back and forth to work. No further records of their activities were maintained. Since the experiment was conducted during the winter and spring months, which in this part of the country affords little opportunity for outdoor work around the home, it was felt that these men changed their activities very little. However, the experiment would have been strengthened by maintaining records of physical activity other than the regularly supervised exercise.

If the subject was assigned to the exercise regimen, a program of activities was prescribed after consultation with the examining physician. The exercise program consisted of two phases: an individual program outlined to meet the specific needs of each subject and a general program in which all subjects followed a single exercise routine. However, the emphasis in the exercise phase of the study was placed on the supervised portion participated in by all subjects as soon as they were considered physically capable. At the start, all subjects were cautioned against all-out efforts in any of the exercises for several weeks. The program was a supervised noon-hour calisthenics-swimming class to which the subjects reported as often as possible Monday through Friday.*

Under supervision the group performed six calisthenic exercises for one minute each. The number executed during the one-minute period was recorded daily. Following the calisthenics the subjects swam in the pool. The number of laps which could be swum continuously was recorded daily. Most of the subjects had difficulty swimming more than two or three laps (25 yards per lap) at the beginning, whereas three months later they were routinely completing 20 to 30 laps. A record of attendance at the noon-hour supervised programs was kept for each subject, and the means and ranges in attendance are presented in Table I. There were days when circumstances prevented the subjects from reporting. These absences were included in computing the averages and, of course, resulted in lower means than would otherwise have been the case.

TABLE I

Frequency of Participation in Supervised Exercise Program

	General exercise group		
	First period: January–March	Second period: April–June	Select group: January–June
Number of subjects	7	9	4
Frequency per week			
Mean	2.70	2.58	2.56
Range	2.2–3.6	2.0–3.4	2.0–3.1

The exercise program employed in this study represents about what is possible in an ordinary routine. It would be difficult for the average man to maintain an exercise schedule of more than two or three one-hour exercise periods per week. No doubt greater conditioning would have been achieved if the men had been exercising more often, but such an artificial program would have indicated little of the effect of a practical exercise schedule. From the standpoint of medical considerations, it is also necessary to approach regular exercise moderately at first when dealing with middle-aged men who are used to a sedentary life.

RESULTS

Student's t distribution was employed in studying the changes in the various electrocardiogram measurements. The t's comparing the differences in the changes between the exercise and control groups ranged from -1.07 to $+1.73$, none of which was significant at a probability of 0.10 or less. None of the 5 high blood cholesterol subjects individually showed a significant change.

* One subject could not be present at the noon hour and a gymnasium-type program was carried on instead.

TABLE II

Changes in Total and Free Blood Serum Cholesterol in Normal Subjects

Group	No.	Age mean and (range)	Mean total blood cholesterol (mg/100 ml)			Mean free blood cholesterol (mg/100 ml)			Mean body weight change[b] (kg)
			Before	After	t[a]	Before	After	t[a]	
Exercise	13	43.1 (32–54)	189.5	187.1	0.20	63.0	58.1	0.91	−0.6
Control	13	40.5 (31–51)	194.6	196.6	−0.16	63.5	63.9	−0.08	−0.9
Select	4	42.8 (38–48)	175.3	173.6	0.06	57.9	55.8	0.16	−1.2

[a] None of these Student t's were significant at the 5% level.

[b] Number of subjects for weight change respectively: exercise, 12; control, 8; select, 4.

In the present study, there were no appreciable differences in blood serum cholesterol between the mean initial and final values in either the "normal" control group or the "normal" exercise group (see Table II). This was true also for the four "normal" subjects in the select group who were studied for a total period of six months.

When the difference between the exercise and control groups was analyzed, statistically insignificant Student t values of 0.43 ($p = 0.7$) for changes in total blood serum cholesterol and 1.09 ($p = 0.3$) for changes in free blood serum cholesterol were obtained.

The decrease in total and free cholesterol among those with "high" levels is shown in Figure 1. However, because of the small number of such cases and because the controls as well as exercise subjects showed a decrease, each individual subject was studied further. The analysis appears in Table III. The intra-individual variance used in determining the Student t values was the variation between blood samples taken about one week apart at a testing period. This was compared to variations in mean values between two testing periods. As can be seen in the table, one of the three exercise subjects showed a statistically significant decrease ($p < 0.05$), while none of the controls showed a significant decrease.

Because some of the normal subjects on exercise showed no decrease or even an increase in blood cholesterol and because in some of the controls a decrease occurred, change in body weight in the subjects was studied. Table II reveals that the mean weights of both normal cholesterol groups decreased. The difference in weight loss was not significant ($t = 0.32$). Although members of the control group were not taking regular exercise, the fact that they were participating in the experiment perhaps made them more conscious of their general physical fitness and may have resulted in a limited amount of dieting. Evidence for this is contained in Figure 2, where weight changes of the subjects in all groups are plotted against changes in total serum cholesterol. The subject showing the largest *increase* in blood cholesterol was in the exercise group. This discrepancy and the others can now be understood by the statistically significant correlation ($p < 0.01$) between cholesterol change and body weight change. The high blood cholesterol subjects are also plotted on this graph. The three high cholesterol subjects on exercise lost on the average 1.8 kg of body weight as com-

TABLE III

Changes in Total and Free Blood Serum Cholesterol in Initially High Level Subjects

Subject	Age	Total blood cholesterol (mg/100 ml)				Free blood cholesterol (mg/100 ml)				Body weight change (kg)
		Before	After	t	p	Before	After	t	p	
1 (Exercise)	38	261.0	236.9	1.32	0.29	115.4	97.7	1.62	0.21	−2.6
2 (Exercise)	35	216.6	167.9	2.56	0.07	66.3	45.9	2.96	0.04	−1.4
3 (Exercise)	32	224.7	193.2	1.86	0.15	61.7	57.2	0.64	0.28	−1.4
4 (Control)	35	239.3	216.6	1.29	0.27	84.1	66.3	1.58	0.19	−3.5
5 (Control)	31	258.1	247.7	0.30	0.40	100.3	93.3	0.82	0.45	0.0

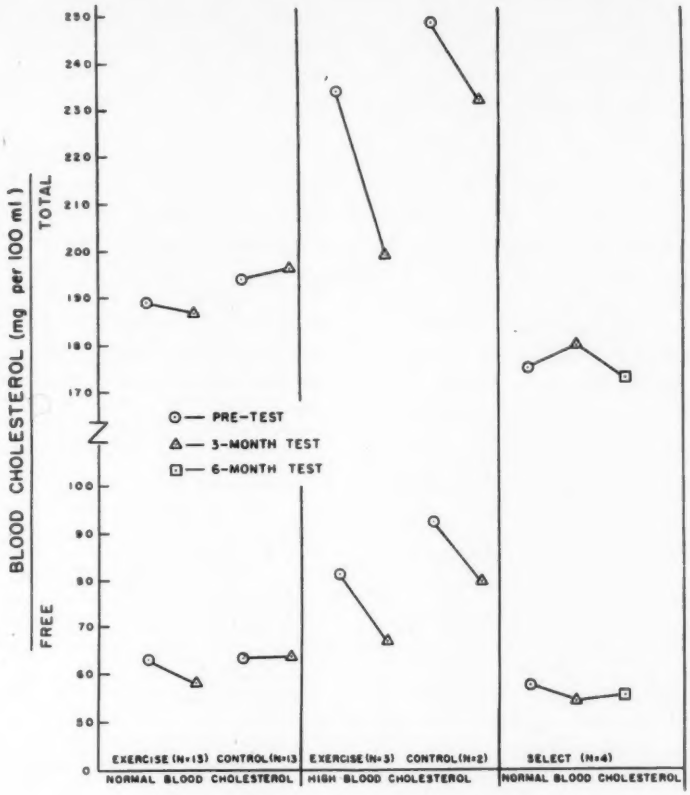

Fig. 1. Changes in blood serum cholesterol.

pared to a mean of 0.6 for the entire exercise group. These subjects also showed above-average decreases in blood cholesterol. The one high-cholesterol control subject whose cholesterol was lowered considerably (subject 4, Table III) lost 3.5 kg of body weight as compared to 0.9 kg for the entire control group. The other high-cholesterol control whose level did not change appreciably (subject 5, Table III), did not change in body weight.

It is unfortunate that accurate diet recall records were not available on the subjects. However, it is doubtful that the percentage of fat or cholesterol in the diets was changed appreciably because the men were all eating at home, they were cautioned not to change their dietary habits, and the experiment was of short duration. If the decrease in blood cholesterol in some subjects is to be attributed to changes in diet, this factor should also be responsible

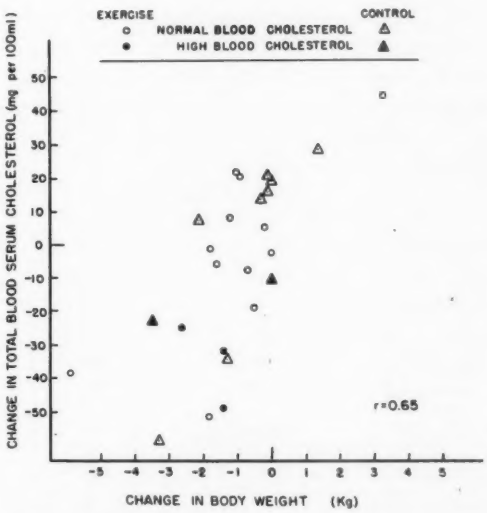

Fig. 2. Relationship between change in blood serum cholesterol and change in body weight.

for the increases in the remaining subjects (almost half of the total). This does not appear logical, although without substantiating diet records, it cannot be ruled out as a possibility.

Changes in free cholesterol were also plotted against weight change and, although the trend was similar to total cholesterol, the relationship was not as close ($r = 0.41$, $p = 0.05$). A ratio of total to free cholesterol was computed for each subject at each testing period. The changes in these ratios were plotted against weight changes, but no statistically significant trends were observed ($r = 0.23$, $p = 0.10$).

In view of the small number of cases, the results should not be considered conclusive. Nevertheless, the results (see Fig. 2) suggest that the effects of exercise are indirect in that they are present only when associated with a weight loss. This agrees with the work of Mann,[8] whose subjects were overfed without exhibiting an increase in blood cholesterol provided the daily energy expenditure was increased sufficiently to compensate for the increased food intake. It also explains why Taylor and collaborators[9] found no significant change in blood cholesterol in subjects who exercised but who were maintained in caloric balance. It is unfortunate that other human studies and those with animals did not include data on body weight or fat changes.

It is possible that a closer relationship could be shown between changes in total serum cholesterol and change in body fat than with body weight in the present study, but it was not possible to secure accurate specific-gravity data on the subjects.

The relatively simple explanation of cholesterol change suggested here probably does not explain the abnormal lipid metabolism which occasionally appears. However, it is not out of line with the data utilized by insurance companies for many years which show clearly a correlation between excess body weight and incidence of heart disease.

SUMMARY

The effects of supervised exercise (three months) on total blood serum cholesterol were studied among 31 sedentary middle-aged men. No effect was observed among subjects with "normal" initial serum levels. However, three "high" level subjects showed an appreciable decrease following exercise compared with two controls with high initial levels. When the subjects of both groups were combined, change in total serum cholesterol generally accompanied a change in body weight regardless of whether the subject was in the exercise or control group. Exercise, therefore, was effective in decreasing total blood serum cholesterol in some subjects, but this effect appeared to be indirect by decreasing body weight. Free serum cholesterol showed the same trends, but the relationship with body weight changes was not as close.

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Nutritional Factors in Liver Disease in Man

A Review

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ALTHOUGH fatty liver, hepatic necrosis, cirrhosis, and hepatic neoplasms may be readily produced in the experimental animal by dietary deficiency, it has been difficult to apply these findings to man. The etiologic relationship of malnutrition to liver disease in human subjects has been largely investigated by correlating dietary histories with histopathologic studies of autopsy or biopsy material and observations on therapeutic response of reversible morphologic lesions to diet, vitamins, and food supplements. These studies have led many to believe that poor dietary habits are directly responsible for the fatty liver-cirrhosis syndrome in man; however, others feel that undernutrition simply predisposes the liver to injury by endogenous or exogenous noxious substances and is, therefore, only indirectly responsible for hepatic disease.

This paper reviews recorded evidence upon which these postulates are based, reports additional observations from studies on malnourished alcoholic subjects, and discusses the contribution of nutritional deficiencies resulting from hepatic dysfunction to the perpetuation of liver injury.

FATTY LIVER

Dietary deficiency has been more closely related to fatty liver than any other morphologic change of the liver. Rats fed diets deficient in choline and its precursors develop centrilobular fatty infiltrations,[1] whereas rats receiving a low-protein intake and normal choline develop peripheral fatty infiltration.[2] Identical morphologic changes have been noted in man: fatty metamorphosis which begins in the centrilobular area in alcoholic patients with poor dietary habits[3] and fatty changes initially localized to the periphery of the hepatic lobule in malnourished subjects with kwashiorkor.[4] Fat is intracellular and extracellular[5] in distribution, in contrast to the primary intracellular localization of fat often seen in liver injury associated with chemical and heavy-metal intoxication[6] or toxemia of pregnancy,[7] where toxic interference with the enzyme systems necessary for mobilization of fat may occur.

The clinical association between nutritional deficiency and fatty liver is based largely upon dietary histories and therapeutic responses. Controlled observations in human volunteers with normal liver are needed to determine whether feeding an inadequate diet will produce a fatty liver. Isolated opportunities present themselves for such observations in patients with other illnesses. In the Jersey City Medical Center serial biopsies in 2 patients with terminal neoplastic disease, and 1 patient with heart failure whose intake was grossly deficient in protein showed a normal liver initially and fatty liver after a six-week to three-month period of the dietary abnormality. Similar observations have been made in alcoholic patients in which fatty liver has been the only manifestation of disease. Case 1 is illustrative.

CASE 1. A 48-year-old chronic alcoholic was hospitalized in an alcoholic stupor with a history of ingesting 1–2 quarts of whiskey daily for several weeks before admission. Examination revealed hepatomegaly and ankle edema. A liver biopsy showed marked fatty

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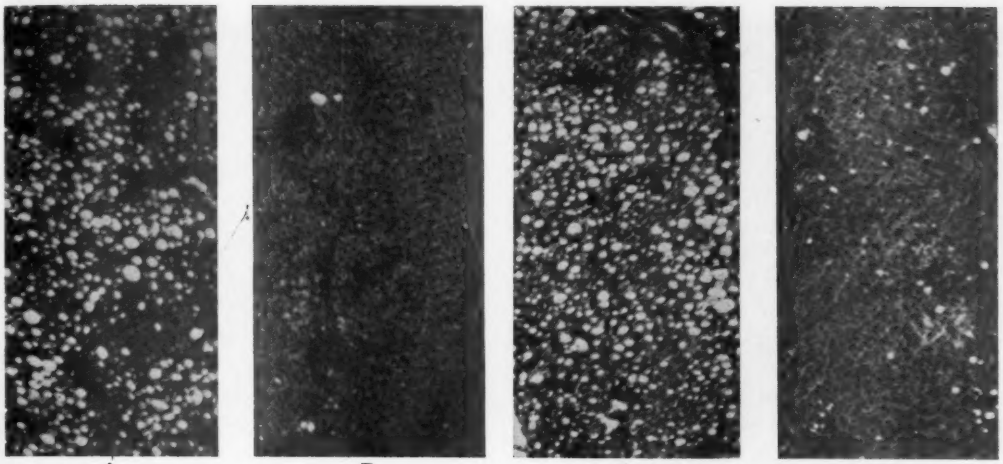


A B C D

Fig. 1. (A) Severe fatty liver associated with normal liver function studies except for bromsulfalein retention 25 per cent. (B) Normal liver after five weeks of therapy; bromsulfalein 3 per cent. (C) Severe fatty liver after five weeks of alcoholism; bromsulfalein retention 17.5 per cent. (D) Normal liver after six weeks of treatment; bromsulfalein 0.

liver (Fig. 1*A*). The patient received a diet of 350 g of carbohydrate, 175 g of protein, and 60 g of fat with supplemental choline, methionine, and multivitamins. A repeat biopsy in five weeks was normal (Fig. 1*B*). He was discharged and consumed the same quantity of alcohol each day, eating bread and other starches occasionally. A repeat biopsy in five weeks showed a return of severe fatty metamorphosis (Fig. 1*C*) which again responded to dietary therapy (Fig. 1*D*).

It is difficult to incriminate dietary deficiency alone as the cause of fatty liver, as it usually accompanies alcoholism,[8] diabetes,[9–11] obesity,[12] cystic fibrosis of the pancreas,[13] heart disease,[14] and other conditions. These diseases may alter intermediary metabolism and thereby predispose to steatosis of the liver. Nevertheless, dietary histories in patients with fatty liver and these conditions show a good correlation between protein intake and severity of fatty liver.[15] Also, a deficiency of dietary protein contributes to the fatty liver in kwashiorkor. The liver of the newborn and nursing infant in areas where this disease is endemic is normal,[16] but during the weaning period, diets are consumed which are grossly deficient in protein. This produces atrophy of the enzyme-secreting glands of the pancreas, small intestines, salivary and lacrimal glands, and secondarily causes hepatic, dermal, and cerebral lesions.[16]

Role of Alcoholism

The occurrence of fatty liver in so many different disease states has led many to question the role of a nutritional disturbance in its production. Indeed, studies of both malnourished war prisoners and infants without other diseases have revealed an atrophic, nonfatty liver.[17] Most controversy has arisen relative to the role of alcoholism in the development of fatty liver. Alcohol could produce a fatty liver by supplying a high-carbohydrate intake without sufficient protein, vitamins, and other essential nutrients or could interfere with enzyme systems and alter metabolic pathways which are responsible for fat removal. The capacity of alcohol to enhance the hepatotoxic effect of carbon tetrachloride, phosphorus, and other agents is well known.[18] Acute administration of ethanol in noncholine-deficient rat causes an increase in total liver lipids without decline in hepatic lecithin, presumably due to a toxic effect.[19] Animal experiments demonstrate that alcohol creates a nutritional imbalance, as it does not spare nitrogen on low-protein diets. In choline-deficient rats, it produces no greater degree of fatty metamorphosis than an isocaloric equivalent of sucrose.[20]

Clinical studies in alcoholic patients support

the thesis that alcohol per se does not predispose to fatty liver, as there is no correlation between the degree of steatosis and the amount, duration, or type of alcoholic intake in patients with similar dietary habits.[21] Several investigators have attempted to evaluate the effect of alcohol on patients with cirrhosis or fatty liver.[22] None of the reported studies have demonstrated deleterious effects of alcohol in the amounts used; however, the quantity of alcohol ingested was quite small in comparison to the amounts consumed by the typical alcoholic hospitalized with fatty liver (see case 1). Furthermore, the diets employed were much better than those ingested by most alcoholic subjects on a drinking spree.

The frequent absence of apparent hepatic abnormalities in alcoholic patients has been cited as favoring a constitutional predisposition to fatty liver and cirrhosis.[23] Biopsy study frequently reveals unsuspected liver disease. Two-thirds of alcoholic patients hospitalized with delirium tremens have histologic evidence of liver disease.[21] As yet unexplained is the finding of normal liver biopsies in some alcoholic subjects with poor dietary habits who exhibit other signs of malnutrition.

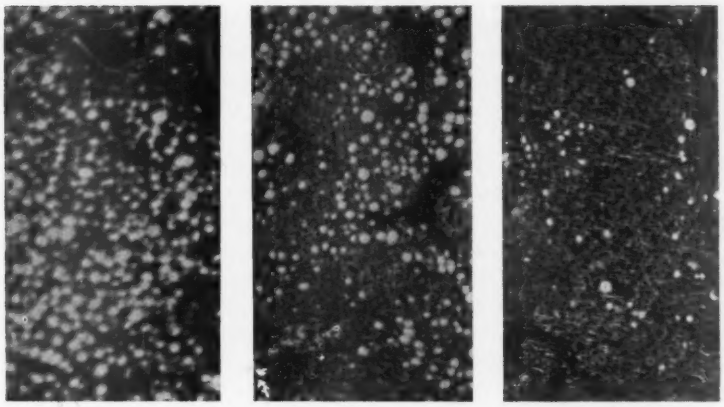
Role of Lipotropic Agents and Protein

Response of human fatty liver to lipotropic agents has been used as evidence that a deficiency of these substances is responsible for this condition.[24–27] In vitro studies suggested that these substances are necessary for transport or oxidation of fat and thereby gave impetus to the theory that fatty liver represents a deficiency state resulting either from dietary lack or mechanisms interfering with use of fat-removing substances. Choline enhances oxidation of fatty acids added to tissue in vitro;[28] however, in vivo studies using D_2O and C^{14} acetate failed to demonstrate an increase in fatty acid oxidation.[29,30] The exact mechanism of choline in influencing fatty liver has been questioned, since adding cystine or alpha-tocopherol or raising the level of dietary protein without lowering available methionine and cystine will also enhance fatty acid oxidation.[31] Animal studies suggest specific protein differences unrelated to the choline system; alteration of intestinal activity, an abnormality of endogenous fat metabolism, or other process may account for fatty liver.[32] It has been demonstrated that nonabsorbable antibiotics added to a choline-deficient diet prevent development of fatty liver,[33] indicating either a choline-sparing activity of the antibiotics or the elimination of an as yet undefined factor which is necessary in addition to a lack of choline for production of fatty liver.

Clinical studies show that diets containing adequate protein but deficient in choline are effective in kwashiorkor, whereas choline alone is not helpful.[4] Variable therapeutic results have been achieved in alcoholic patients with fatty liver, depending upon the degree of steatosis. To standardize results, only severe fatty liver should be used in therapeutic studies. Any adequate diet will cause the severe fatty liver of malnourished alcoholics to return to normal within four to six weeks. Addition of vitamins, lipotropic agents, vitamin B_{12}, sex hormones and other supplements will not accelerate removal of fat, indicating that time is as important as the therapeutic program.[15]

Attempts have been made to evaluate the role of lipotropic agents in producing fatty liver in man by comparing the effects of a choline-deficient and a normal diet in the same patient. Alcoholic subjects had no significant changes in severe fatty metamorphosis when fed a diet inadequate in protein and choline, whereas addition of choline or protein caused decrease or disappearance of fat.[34–36] As indicated by the investigators, these studies cannot be interpreted as indicating that a specific dietary deficiency produced or perpetuated the fatty changes.

In our experience, no dietary regimen will cause severe fatty liver to change significantly during the first two weeks of therapy, and all programs tested to date, including a low-protein, choline-deficient diet, have been effective in the malnourished alcoholic in four to six weeks.[37] Pharmacologic studies which demonstrate dimethylaminoethanol to be a more effective precursor of acetyl choline than exogenous choline[38] suggest that endogenous supplies of choline and other lipotropic agents in man may cause disappearance of fatty liver.[39]



A B C

Fig. 2. (A) Severe fatty liver. (B) Moderate fatty liver after three weeks of therapy on a hypolipotropic, low-protein, high-carbohydrate diet. (C) Normal liver after six weeks on a hypolipotropic, low-protein, high-carbohydrate diet.

The following case history illustrates the mobilization of liver fat over a six-week period of treatment in which the diet was inadequate in both choline and protein.

CASE 2. M. A., a 44-year-old housewife with a history of chronic alcoholism, was first seen in 1948 because of sensorial disturbances incident to hypoglycemia. Examination revealed an enlarged liver; biochemical study demonstrated an elevated serum bilirubin and increase in serum globulin. A liver biopsy showed severe fatty metamorphosis. During the next 6 weeks she was given a diet of 350 g carbohydrate, 125 g protein, and 100 g fat. A repeat biopsy at the end of treatment showed no fat.

Upon discharge, the patient returned to alcoholism and a poor diet and was rehospitalized on two occasions with fatty liver. On her third readmission with severe fatty liver (Fig. 2*A*), the patient was put on a daily diet with supplemental glucose infusions calculated to provide less than 100 mg choline and 20 g protein. On this regimen there was a moderate decrease in fat in three weeks (Fig. 2*B*) and complete disappearance in six weeks (Fig. 2*C*).

The high incidence of fatty liver in obese subjects whose diet is frequently high in carbohydrate and low in protein has suggested the presence of a relative deficiency of lipotropic factors in this state.[12] Occasionally fatty liver in obese patients is refractory to a high-protein, high-choline intake, whereas with adequate weight reduction it disappears.[40] In diabetes, fatty liver also may not respond to diet unless insulin is also given.[41]

It is felt by some that fatty liver may be an incidental finding and does not reflect the basic morphologic alteration of malnutrition. It is of considerable clinical significance, as in severe phases fatty liver may be accompanied by marked biochemical dysfunction and evidence of liver failure[15] including icterus, fluid accumulation, sensorial changes, and portal hypertension,[42] all of which disappear with mobilization of fat. Moreover, three-fourths of alcoholic patients with severe fatty liver in whom the pathogenetic mechanism leading to fatty liver is permitted to continue will develop cirrhosis, but early recognition and proper treatment with an appropriate diet will cause complete restoration of a normal cellular pattern.[15]

LIVER-CELL NECROSIS

Liver-cell necrosis may be produced in experimental animals by diets deficient in cystine, vitamin E, and factor 3.[43–45] There is interference with the oxidative enzyme processes related to an inadequate intake of selenium.[46] The lesion may be localized or massive, depending upon the severity of the dietary deficiency.[47] Search for a comparable lesion in malnourished human subjects has been fruitless, comparable histopathologic lesions being noted only in subjects with viral hepatitis[48] or chemical intoxication.[49] Focal necrosis and inflammation were the only abnormality noted in 10

per cent of malnourished alcoholic patients studied by biopsy in the Jersey City Medical Center. This lesion does not appear to be specific and may be seen after removal of fat and during the recovery phase of viral and toxic hepatitis. Serial biopsies have not demonstrated a transition of this lesion into cirrhosis in any instance.

Simple necrosis is commonly seen with fatty liver, and hyaline necrosis is often present in the cirrhotic patient hospitalized after an acute episode of alcoholism.[50] Hyaline necrosis was originally considered as pathognomonic of alcoholic cirrhosis, but we have also noted it in biopsies from diabetics without a history of ingesting alcohol and in patients who have developed gastrointestinal hemorrhage or infections on a hospital regimen for several months. Occurrence of hyaline necrosis in monkeys maintained for long periods on choline-deficient, low-protein, high-cholesterol diets[51] strongly suggests that this lesion is due to biochemical alterations attendant on nutritional deficiency. This lesion is usually associated with sensorial changes, fluid retention, icterus, abnormal liver-function tests, and leukocytosis. As a group, these patients respond poorly to therapy and require special supportive measures.

Nutritional deficiency appears to predispose the liver to necrosis from noxious substances. It has been suggested that regardless of its etiology an imposed biochemical deficiency is responsible for death of liver cells.[47] Malnourished subjects appear to be more susceptible to fulminant hepatitis of viral origin[48] and to hepatic lesions in carbon tetrachloride intoxication.[52] Since host resistance to necrogenic agents, a major determinant of the degree of injury, is so variable, it is quite difficult to be certain of the specific role of dietary abnormalities.

CIRRHOSIS

The relationship of poor nutrition to cirrhosis is based on the following points:

(1) The experimental observation that continuation of choline or protein deficiency in animals which develop fatty liver ultimately causes diffuse hepatic fibrosis and cirrhosis.[53,54]

(2) The occurrence of postnecrotic scarring following diet-induced necrosis in rats.[47–55]

(3) Demonstration of transition of fatty liver in the alcoholic[15,37] and diabetic[41] to Laennec's cirrhosis by serial liver biopsies.

(4) Development of hepatic fibrosis with continuation of the pathologic process leading to fatty liver in kwashiorkor.[16,56]

Two anatomically distinct types of cirrhosis have been demonstrated—a diffuse finely granular cirrhosis (Laennec's cirrhosis) and a coarse nodular cirrhosis (postnecrotic scarring[57]). In experimental animals choline deficiency ultimately leads to diffuse fibrosis,[53] whereas a deficiency of sulfur-containing amino acids or vitamin E is followed by postnecrotic cirrhosis.[59] Laennec's cirrhosis is the common form of cirrhosis seen in malnourished man, and postnecrotic scarring, although frequently of unknown origin, appears to develop following toxic liver injury. It is usually impossible to clinically distinguish the forms of cirrhosis and oftentimes a combination exists.[60]

Cirrhotic Transition of Fatty Liver

Although mechanisms responsible for development of cirrhosis in patients with fatty liver are not clear, and, therefore, poor nutrition may only provide a setting for whatever process leads to cirrhosis, *it is certain that continued poor dietary habits which initially produced fatty liver will ultimately lead to a fibrotic liver.*[61] Postmortem observations[62] and reconstruction studies[63] suggested this sequence of events, and proof was provided by serial liver biopsies in alcoholic subjects.[15,64] Of 20 patients with severe fatty liver, repeat studies showed normal liver in each of 11 patients who discontinued their alcoholism and poor dietary habits; cirrhosis developed in 7 patients (Fig. 3) and fatty liver persisted in 2 who continued alcoholism and poor diets. Case 3, which is representative of this group, provides good evidence that continuation of the factors responsible for fatty liver eventually leads to cirrhosis.

Case 3. L. B., a 54-year-old housewife, was hospitalized because of chronic alcoholism associated with a very poor dietary intake, principally carbohydrates. There was evidence of recent weight loss, anemia, an

TABLE I
Biochemical Alterations with Transition of Fatty Liver to Cirrhosis

	Before therapy	After therapy	4 yr later	6 yr later
Biochemical study				
Serum bilirubin (mg %)	0.3	0.1	2.2	27.2
Bromsulfalein (%)	6	0	32	—
Serum alkaline phosphatase (B. U.)	2.3	2.6	6.5	4.5
Total serum cholesterol (mg %)	171	210	132	343
Cholesterol esters (mg %)	82	150	79	126
Serum albumin (g %)	3.1	4.2	2.5	2.8
Serum globulin (g %)	3.1	2.9	5.0	3.5
Cephalin flocculation	1+	0	2+	4+
Thymol turbidity (units)	1.0	1.0	5.0	5.0
Histologic study				
Fibrosis	0	0	2+	3+
Fat	3+	0	0	0
Regeneration	2+	1+	3+	3+
Bile stasis	0	0	1+	2+
Infiltration	1+	0	2+	2+
Necrosis	0	0	0	1+
Other	0	0	0	0
Pathogenic diagnosis	Fatty liver	Normal liver	Moderate cirrhosis	Severe cirrhosis

enlarged liver, and a smooth red tongue on examination. Biochemical liver-function tests were normal except for a slight elevation of serum globulin (Table I); a liver biopsy showed severe fatty metamorphosis without fibrosis (see Fig. 3).

A six-week period of rest and a general hospital diet caused the disappearance of all clinical, biochemical, and histologic abnormalities. The normal lobular pattern could be demonstrated on repeat liver biopsy.

After discharge the patient returned to alcoholism and consumed 1–2 quarts of whiskey and/or wine daily, eating only bread and other starches, rarely eating meat, fruit, or vegetables. She was rehospitalized four years later with signs of liver failure. Marked pallor, slight icterus, spider angiomas, splenomegaly, ankle edema, cheilosis, and peripheral neuropathy were present on examination. Liver function tests showed elevated bilirubin and bromsulfalein retention and a low serum albumin. A repeat liver biopsy showed fibrosis, pseudolobulation, bile stasis, and inflammation (see Fig. 3). Hematologic study demonstrated a moderate macrocytic hemolytic anemia. The patient responded to a regimen of bed rest, diet, vitamins, glucose infusions, and whole-blood transfusions given over a three-month period.

After discharge she promptly resumed her alcoholism and poor dietary intake. She was rehospitalized two years later with icterus, ascites, ankle edema, hepatic fetor, hematemesis, and sensorial changes. Biochemical tests showed further impairment of hepatic functional reserve. There was no response to therapy. Postmortem studies showed marked cirrhosis with severe fibrosis, nodular regeneration of liver cells, hyaline necrosis, bile stasis, and inflammation in the connective tissue stroma (see Fig. 3).

Considerable attention has been directed to the possible mechanism by which a fatty liver undergoes fibroblastic transformation and eventually produces the lobular distortion characteristic of cirrhosis. Based on animal studies,[5,54,65] postmortem observations,[57,66,70] and liver biopsies,[15,37,57] the following sequence has been postulated to be responsible for liver fibrosis which appears in fatty liver: conglobation of intracellular fat leads to large fat globules which displace the liver cell nucleus and merge to form fatty cysts. These fatty cysts rupture with a continuation of the pathologic process, and their collapsed walls, which consist of reticulum, constitute the beginning of the fibrotic process. Fibroblastic activity is often noted in the surrounding area of inflammation and may be responsible for converting a localized process into a diffuse one. Connective tissue changes are accompanied by both duct proliferation and development of new blood vessels which form arteriovenous

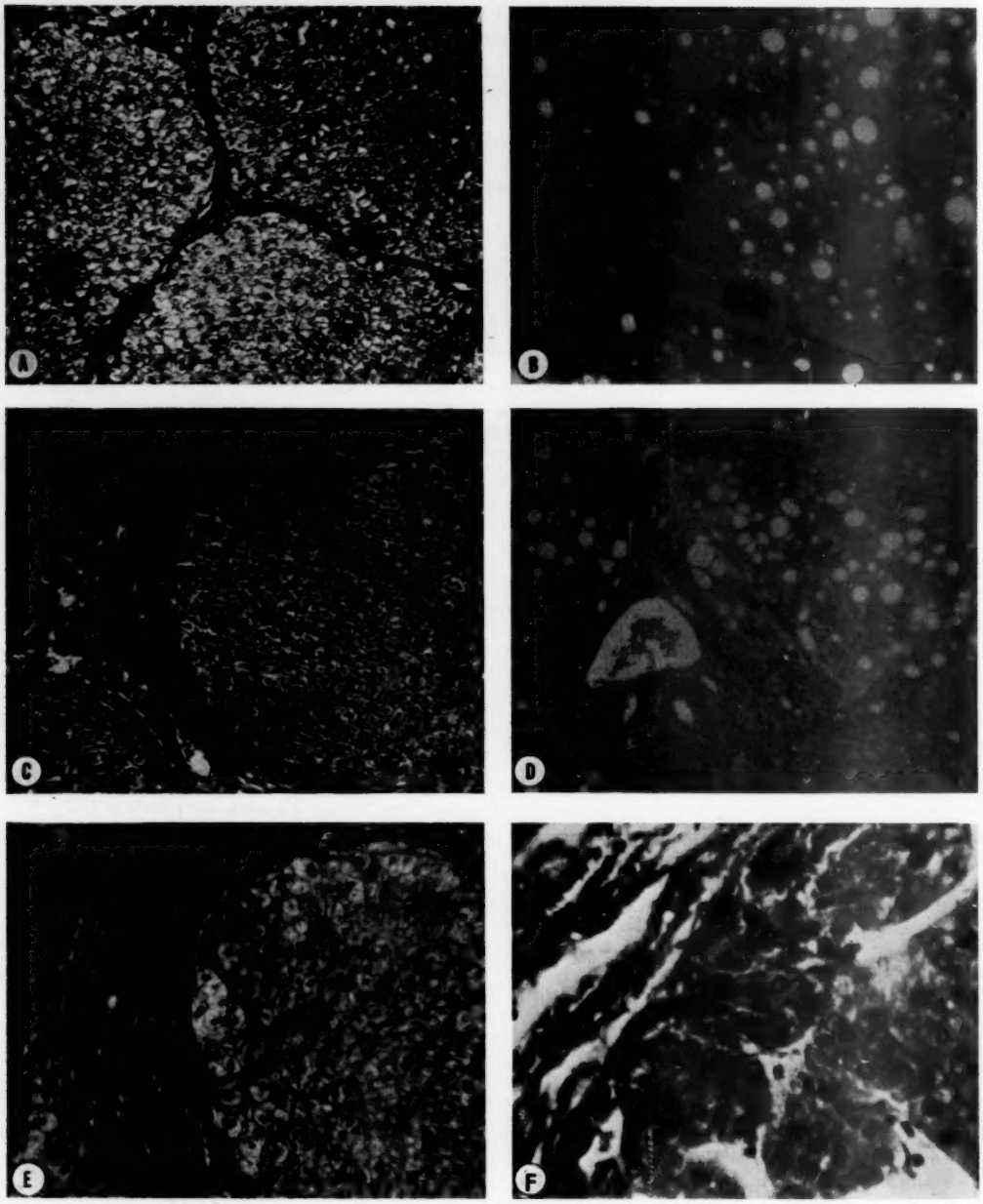


Fig. 3. Stages in fatty liver-cirrhosis syndrome from serial liver biopsies in 43 patients. Eight patients had transition of fatty liver without fibrosis to (A) mild cirrhosis or (B) mild cirrhosis with fat. Fifteen patients observed with transition of mild cirrhosis to (C) moderate cirrhosis or (D) moderate cirrhosis with fat. Twenty patients with moderate cirrhosis observed with transition of moderate cirrhosis to (E) severe cirrhosis or (F) severe cirrhosis with primary liver-cell cancer

anastomoses. Concomitant destruction of liver cells leads to new liver cells which are two to three cell layers thick, in contrast to the normal unicellular liver cords. Repeated episodes of fatty metamorphosis and inflammation are followed by transition of mild and moderate to severe cirrhosis (Figs. 3 and 4), as illustrated by case 3.[57,64]

Kwashiorkor

There is a much less certain relationship between fatty liver of kwashiorkor and cirrhosis. The lack of documented evidence from liver biopsies that hepatic steatosis in this disease is a precursor of the fibrotic liver has cast doubt upon the nutritional origin of cirrhosis. Failure to demonstrate by further observations that kwashiorkor can eventually lead to cirrhosis would make it necessary to seek explanations other than malnutrition for this disease. Epidemiologic studies favor causal relationship and show that the geographic distribution of kwashiorkor in infancy is parallel to that of cirrhosis in adults in Africa.[71] Reconstruction studies suggest that progressive fatty metamorphosis in kwashiorkor eventually leads to an infiltration of the portal triads by round cells, and the fine fibrosis which appears around the periphery of the lobule may be the precursor of diffuse fibrosis.[2]

Viral and Parasitic Infestations

It has been suggested that a viral or parasitic infestation coupled with malnutrition may be responsible for cirrhosis.[17] The hypothesis that a virus which causes liver-cell necrosis and inflammation and ultimately leads to cirrhosis in the presence of undernutrition is quite attractive and would explain the variable incidence of cirrhosis in malnourished subjects. Serial biopsies have demonstrated cirrhosis identical to that seen in malnourished subjects as a sequel of viral hepatitis.[72,73] However, the incidence of this disease in patients with proved viral hepatitis is quite low.[74] The apparent rarity of viral hepatitis in patients with documented cirrhosis has been cited as evidence in favor of immunity imposed by a previous attack of hepatitis, but our observations suggest that the cirrhotic patient is as susceptible to this disease as others. Finally, it seems improbable that the progressive liver damage seen with periods of alcoholism and poor diet can be attributed to an activation of a micro-organism.

Bacteria, spirochetes, protozoa, and metazoa which affect the liver produce granulomas which in combination with malnutrition could cause cirrhosis. Brucellosis,[75] tuberculosis,[76,77] and syphilis[78] may be associated with fatty or fibrotic liver jointly produced by the organism and by dietary habits. In schistosomiasis, deposition of the ova in the portal vein may lead to a vasculitis, a granulomatous reaction, and fibrosis in the portal area.[79,80] Clonorchiasis is likewise associated with a primary lesion of the liver with inflammation of the bile ducts, periportal inflammation, and fibrosis.[81] Such lesions coupled with malnutrition may be responsible for a high incidence of cirrhosis in areas where these infestations are endemic. Amebiasis,[82,83] malaria,[17] and typhoid fever,[37] which are frequently accompanied by inflammatory changes of the liver, may be rarely followed by cirrhosis. Prolonged anorexia, fever, and toxicity, with resulting nutritional imbalance, undoubtedly contribute to hepatic dysfunction.

Chemical Factors

The increased susceptibility of malnourished subjects to chemical injury of the liver has raised the question of the possible role of an unidentified chemical in the development of cirrhosis. This possibility has been most fully explored in alcoholic subjects, as histories of alcoholism and malnutrition are so frequently found in patients with cirrhosis.[84,85] Recently, attention has been focused on chemical injury as the cause of veno-occlusive disease where ingredients used in bush tea in a setting of malnutrition cause endophlebitic thickening, fibrosis, and eventual obstruction of hepatic vein branches.[86–88] Hepatic fibrosis which follows the chronic ingestion of arsenic[89] and other drugs[90] may also be related to nutritional disturbances.

Disturbance in Iron Metabolism

The role of poor nutrition in the develop-

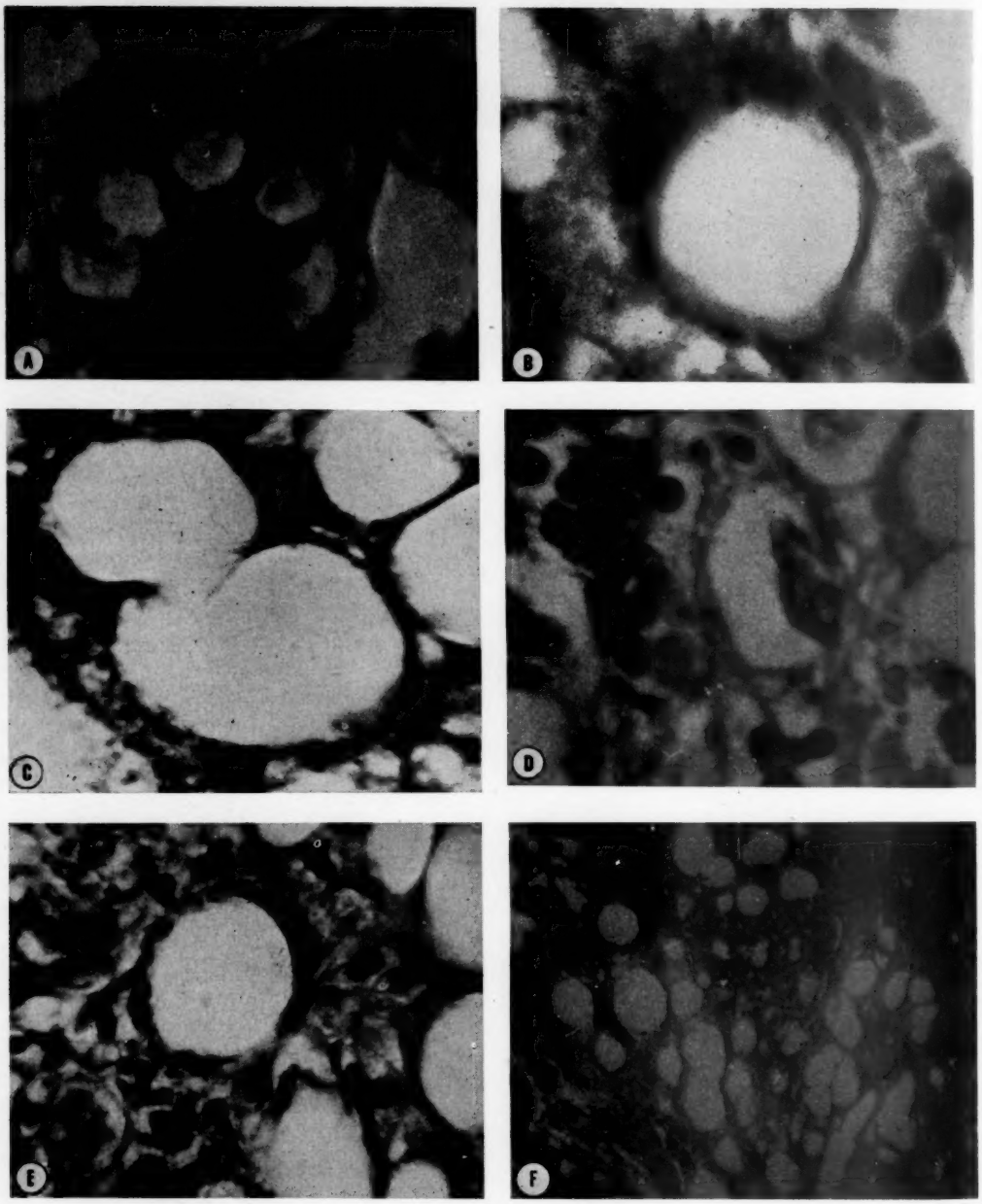


Fig. 4. Cellular changes observed in serial liver biopsies of eight patients with fatty to fibrotic liver. (A) Intracellular fat droplets with central nucleus intact. (B) Large intracellular fat globules with eccentric nucleus. (C) Merging of intracellular fat to produce fatty cyst. (D) Rupture of fatty cyst with collapse of reticulum leading to septum formation. (E) Inflammatory reaction around ruptured fatty cyst. (F) Area showing collapsed fatty cysts and marked inflammation within a fibrous septum. Fibroblasts are present in the connective-tissue stroma.

ment of hepatic fibrosis in iron deposition, glycogen-storage disease, hepatolenticular degeneration, and the lipidoses has been extensively studied. It has been suggested that malnutrition is responsible for hepatic fibrosis in iron-storage disease, as excess liver iron is not followed by cirrhosis in properly nourished animals[91] but causes a lesion identical to hemochromatosis in man when coupled with malnutrition.[92] Concomitant hemosiderosis and hepatic fibrosis occur in primary liver disease when there is a disturbance of intracellular metabolism of iron which permits its accumulation in the parenchymal cell;[93] after repeated whole-blood transfusions or infusion of iron in a patient with liver disease;[94] and in hemochromatosis or acquired defects in intestinal absorption of iron.[95,96] Malnutrition may contribute to the development of liver fibrosis in any of these conditions. The lack of correlation of the degree of fibrosis and iron deposition in either cytosiderosis seen in Africa,[96] hemochromatosis,[97] or transfusion hemosiderosis[98] suggests that the fibrosis may not be related to a disturbance in iron metabolism and that some other factor such as malnutrition is responsible for connective tissue changes. Hepatic fibrosis has been noted in glycogen-storage disease associated with a deficiency of both branching and debranching enzymes.[99] The presence of an inborn error of copper metabolism in Wilson's disease is accompanied by aminoaciduria and ultimately leads to postnecrotic cirrhosis. Further study is desirable to determine whether this lesion is due to the effects of abnormal copper metabolism, protein wastage, or other undefined mechanisms.[100–102]

Therapeutic Effects

Therapeutic studies of cirrhosis which show a marked clinical improvement with a nutritious diet[103] are frequently cited as evidence in favor of a nutritional origin of cirrhosis. An appropriate diet causes mobilization of fat, disappearance of necrosis, and decrease of fibroblastic activity in patients with mild to moderate cirrhosis.[64] Since a similar response occurs with rest and diet in hepatic disease due to toxic and infectious agents, it is not possible to attribute observed therapeutic effects to replacement of deficient nutrients. It also has been demonstrated that improvement is not accelerated by special dietary measures, and similar results will occur on a general hospital diet.[104]

NEOPLASIA

Prolonged choline deficiency in the rat ultimately leads to cirrhosis with hepatoma.[105,106] Neoplasia-like changes are also produced following prolonged administration of ethionine[107] or bentonite,[108] which induce methionine and choline deficiency, respectively. If one accepts the thesis that cirrhosis results from nutritional deficiency it is natural to conclude that primary liver-cell cancer developing in the patient with cirrhosis (see Fig. 3*F*) is a direct result of prolonged malnutrition. Large nuclei seen in the livers of children with kwashiorkor[109] and in adenomatous nodules of malnourished alcoholics with cirrhosis may represent early phases of a neoplastic process. The highest incidence of hepatoma in nontropical countries has been recorded in hemochromatosis,[95] the next highest in postnecrotic cirrhosis,[60] and the least in Laennec's cirrhosis.[110]

Serial studies of malnourished alcoholic patients with cirrhosis reveal no correlation between therapeutic adherence and development of a hepatoma. Five patients who maintained a rigid diet and discontinued alcoholism were observed to develop hepatoma within one to six years of initial observation. The time period was similar in patients who maintained poor dietary intake and alcoholism. These data, coupled with the lack of any increase in incidence of hepatoma in Laennec's cirrhosis, the liver lesion most clearly associated with malnutrition, casts considerable doubt on the role of nutritional deficiency per se in primary hepatic neoplasms.

NUTRITIONAL CHANGES SECONDARY TO HEPATIC DISEASE

While the etiologic relationship of malnutrition to liver disease may be debatable, the usual presence of stigmata of nutritional deficiency in patients with advanced liver dis-

ease is well established. Evidence of altered intermediary metabolism of carbohydrate, protein, and fat; vitamin and mineral imbalance; and clinical manifestations such as hypovitaminosis, osteomalacia, fluid accumulation, parotid gland swelling, and muscle wasting are commonly seen and cited as evidence of a nutritional origin for many instances of chronic liver disease. These changes may be due to dietary inadequacy, abnormal absorption of foodstuffs, or impaired assimilation or utilization of nutrients.

Many of the clinical evidences of malnutrition in patients with liver disease are due to maintenance of poor dietary habits. Occasionally, long-term therapeutic use of a diet restricted in protein, fats, minerals, or vitamins is responsible for a deficiency syndrome. More frequently, the acutely ill patient with ascites, sensorial changes, or jaundice has a poor appetite, and despite continuous efforts even a minimum intake is not obtained. Oftentimes tube or parenteral feeding is necessary to control acute deficiency states while awaiting improvement in hepatic reserve.

Pathologic Effects

Few studies have been conducted on the effects of liver disease on intestinal absorption. Although azotorrhea has been rarely noted, steatorrhea is frequently seen in liver disease.[111] A variety of processes may cause malabsorption in the patient with hepatic disease: decreased elaboration of bile salts or alteration of their chemical composition to reduce emulsification and absorption of fat; deficiency of intestinal and pancreatic enzymes; edema or other morphologic changes of the intestinal mucosa; and portal hypertension or decreased splanchnic blood flow. The decreased absorption of vitamin K and other fat-soluble nutrients in patients with biliary obstruction is well recognized and is frequently treated by parenteral replacements.[112] The contribution of the other processes to encountered deficiencies has, until recently, received little attention. There is often a reduction in pancreatic enzymes in kwashiorkor and other malnutrition syndromes due to the unavailability of protein precursors.[113] This is rarely accompanied by clinical evidence of pancreatic insufficiency.[114]

Malnutrition leads to atrophy and dysfunction of the intestines and produces loss of normal mucosal folds, variability of the caliber of the intestinal lumen, and hypomotility on x-ray.[115–117] We have found typical radiographic changes characteristic of the deficiency pattern in patients with hepatic disease. These changes which disappear on treatment represent functional disturbances due to fatty acids and mucus,[116,117] or actual anatomic changes which are seen on biopsy or postmortem studies in malnutrition. Intestinal alterations are accompanied by decreased absorption of major foodstuffs and, unless recognized and treated, add to impairment of liver function.

Little is known about the effects of intestinal wall changes, portal hypertension, and altered splanchnic blood flow in cirrhosis on absorption and utilization of foodstuffs. The availability of a safe, readily available method of securing jejunal mucosal biopsies[118] now permits a study of morphologic alterations of the intestines in hepatic disease. The effects of altered hemodynamics on intestinal absorption can be evaluated by combining absorption tests with hepatic vein catheterization.[119] Preliminary observations indicate that hepatic uptake of protein and ingested drugs is decreased in patients with cirrhosis and portal hypertension.[120]

Marked alteration in the assimilation and utilization of basic foodstuffs often occurs in cirrhosis due to parenchymal-cell dysfunction or development of arteriovenous and venovenous shunts. In acute liver-cell injury fatty metamorphosis or necrosis is responsible for liver dysfunction. In chronic liver disease progressive fibrosis and nodule formation lead to distortion of the hepatic lobule. Varying functional disturbances occur depending upon the degree and activity of the hepatic changes.[121]

Disturbance in liver-cell function is accompanied by subclinical or clinical alterations of carbohydrate, protein, and fat metabolism.[122] A defect in uptake, storage, or combustion of ingested sugars leads to decreased hepatic

glycogen and disturbances of blood sugar regulation. Occasionally, hypoglycemia with sensorial disturbances[123] or hyperglycemia with glucose, nitrogen, and electrolyte wastage occurs,[124] and contributes further to hepatic abnormalities. Closely related are the decreased gluconeogenesis and reduced protein anabolism which interfere with regeneration of liver cells. Encountered protein disturbances contribute to liver injury by their secondary effects on nutrition. Decreased ability to synthesize albumin leads to hypoalbuminemia and a reduction in colloidal osmotic pressure. This contributes to ascites[125] and mucosal edema, and accentuates nutritional imbalance by interference with appetite and intestinal absorption. Failure of the liver to conjugate ammonia produced by catabolism of protein in the intestines and liver often causes marked mental changes or coma.[126] Attempts to treat the resulting hyperammoniemia with restricted protein intake and antibiotics,[127] although providing better results than sodium glutamate[128] and arginine,[129] induces negative nitrogen balance.[130]

Vitamin deficiencies which are present in most patients with liver disease are sometimes expressions of coenzyme blockage or inability to convert free vitamins into coenzymes owing to deficiency of certain essential substrates.[131] Resulting biochemical defects contribute to intestinal changes,[132] produce sensorial and neurologic changes,[133] and interfere with intermediary metabolic activities dependent upon thiamine, riboflavin, nicotinic acid, pyridoxine and pantothenic acid.[134]

Disturbance of mineral content of the body, frequently found in patients with liver disease, also helps to perpetuate hepatic damage. Excess body sodium, largely due to hyperaldosteronism,[135] is responsible for ascites and its associated debility. Decreases in potassium,[136] magnesium,[137] and calcium[138] causes cerebral and neuromuscular dysfunction and occasionally produces intestinal atony and ileus. Deficient zinc, copper, and other metalloenzymes now recognized to be of vital importance in cell function prevent or delay recovery unless replenished by an appropriate therapeutic regimen.[139]

SUMMARY AND CONCLUSIONS

(1) Malnutrition, often observed in patients with liver disease, may contribute to its development, occur secondary to morphologic changes in the liver, or be unrelated to the hepatic disorder. Nutritional factors appear to be important in development of the fatty liver-cirrhosis syndrome, however. This condition is always seen in the presence of alcoholism, parasitism, or some other pathologic process which alters normal body processes. It is not possible to clearly delineate the individual role of poor dietary habits and other factors in development of hepatic changes.

(2) Utilizing serial liver biopsies in man, it is possible to demonstrate a transition of fatty liver to cirrhosis and eventual development of hepatoma in malnourished alcoholic subjects. The frequent occurrence of this sequence makes it desirable to consider fatty liver as the first stage of cirrhosis, as early recognition and treatment with an adequate diet prevents development of cirrhosis and its complications.

(3) Evidence of malnutrition is frequently found as a secondary phenomenon in the patient with hepatic disease due to decreased intake, abnormality of absorption and/or decreased assimilation and utilization of foodstuffs. Resulting alterations in intermediary metabolism may delay or prevent recovery from hepatic disease.

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Prognostic Criteria of Severe Protein Malnutrition

E. KAHN, M.D., M.R.C.P.E.*

THROUGH ignorance and poverty many African mothers feed their infants and older children on diets consisting almost entirely of maize. Consequently clinical evidence of protein malnutrition (kwashiorkor, sindrome policarencial infantil, distrofia da farinacei) is common in this group of the population. Advanced cases are characterized by nutritional edema and acute nutritional dermatosis, and these patients usually die within days or weeks if left untreated.

Depending on the selection of cases and the methods of treatment the death rate in protein malnutrition ranges from less than 10 per cent in some centers to over 50 per cent in others.[1,2] At Baragwanath Hospital, the mortality in advanced protein malnutrition was 40 per cent when treatment consisted almost entirely in the administration of skimmed milk.[3] It dropped to 20 per cent when intravenous electrolyte therapy was added for the patients showing clinical evidence of dehydration.

During the past three years the mortality in protein malnutrition at this hospital has remained unchanged at 20 per cent. This study was undertaken in an attempt to determine the clinical signs which distinguish the patients who die of the disease from those who survive on our present treatment. An ability to identify such "bad risk" patients on admission to the hospital might enable us to make further progress in the treatment of this very common condition.

MATERIAL AND METHODS

The investigation was based on clinical and certain biochemical data obtained from 100 children admitted to this hospital with the diagnosis of severe protein malnutrition during the winter of 1957. All children showed evidence of nutritional edema and/or acute nutritional dermatosis. The latter was encountered in the various stages of development described by Trowell *et al.*,[4] ranging from the earliest erythematous blotching of the skin which fades on pressure to exfoliating black "enamel paint" plaques with oozing raw surfaces. Patients who did not show evidence of either edema or acute dermatosis were excluded from this series. Fatalities occurring during the first 24 hours after admission to hospital were included, as were all those children suffering from associated debilitating illnesses. The birth date was known in all except three patients.

The clinical and biochemical data in this paper are those found on admission to the hospital unless the contrary is specifically stated. The clinical state of hydration of the patients was judged by the elasticity of a fold of skin raised over the anterior chest wall or the upper abdomen (at other sites edema may interfere with the test). Impaired elasticity, however slight, was interpreted as clinical evidence of dehydration, except in patients with extreme wasting, where looseness of the skin from loss of subcutaneous fat rendered the test valueless.

The body weight and height of the patients were compared with American averages,[5] because reliable data for African children were not available.

Serum sodium and potassium concentrations were measured by flame photometry on venous blood which was withdrawn from the internal jugular vein before the patients had received any intravenous therapy. Blood sugar levels were determined by the "true sugar" colorimetric method.[6] Rectal swabs were taken

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from all patients and were plated on SS agar and desoxycholate citrate agar. The chests were x-rayed, except in a few patients who died shortly after admission to the hospital.

All children were treated with an acidified milk formula containing 3 per cent protein, 4.5 per cent lactose, and 1.3 per cent fat. Milk feeds totaled 150 to 200 ml per kg of body weight per day. Each child was given 50 mg of ascorbic acid per day, but no other vitamin supplements.

Intravenous fluid therapy was used only for dehydrated patients. It was guided, wherever possible, by serum sodium and potassium values. When this information was not available, patients were given our standard electrolyte solution which contains 38 meq/l of sodium, 27 meq/l of potassium, and 65 meq/l of chloride in 5 per cent of invert sugar. During the first 24 hours of intravenous therapy, the patients usually received 200–220 ml per kg of body weight of this solution. In children with acidotic respiration, this was preceded by an intravenous infusion of 0.166 N molar sodium lactate in quantities of 60 ml per kg of body weight. Milk feeds were usually started within 12 hours of commencement of intravenous therapy. During the first 24 hours, feeds amounted to 60–90 ml per kg of body weight. On subsequent days the feeds were increased to about 200 ml per kg of body weight per day, while the volume of the intravenous fluids was correspondingly reduced. No patient in this series received intravenous plasma or blood.

CLINICAL AND BIOCHEMICAL FINDINGS

There were 20 deaths in this series, of which 7 occurred within the first 24 hours of admission to hospital. Clinical and biochemical data of the fatal cases compare with those of the survivors as follows:

Age

Figure 1 shows that the age distribution of the fatal cases did not differ significantly from that of the survivors. Therefore, the patients' age gave no indication of the prognosis.

Growth and Development

Retarded growth was observed in nearly all cases (Fig. 1), the height of the patients being from 2 to 4 inches below the American average; but the degree of retardation was similar in fatal cases and survivors and could not, therefore, be considered to be of prognostic significance.

Figure 1 shows that the body weight of all the patients was below average, despite the fact that 89 of them were edematous. In 15 (75 per cent) of the fatal cases, the weight was

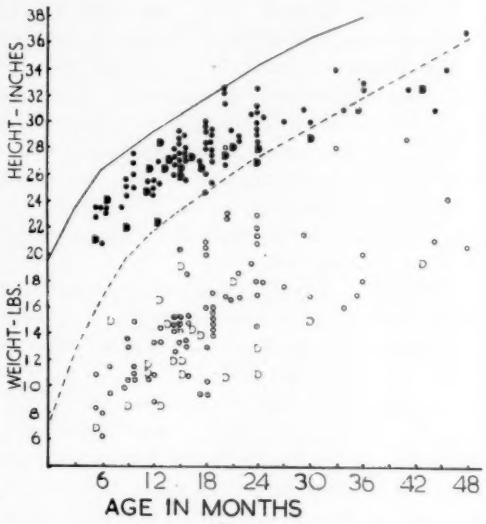

Fig. 1. Height (black dots) and weight (white dots) of patients in relation to age. Fatalities are represented by semicircles. The unbroken line represents the average height of American children, and the broken line the average weight. Five patients, older than 4 years, are not shown.

50 per cent or more below average, whereas this degree of wasting was found in only 24 (30 per cent) of the nonfatal cases. It would appear, therefore, that the prognosis of protein malnutrition is unfavorable if the condition is associated with marked loss of body weight.

Dermatosis

An acute nutritional dermatosis, with or without exfoliation, was a bad prognostic omen. It was encountered in 15 (75 per cent) of the fatal cases but in only 38 (48 per cent) of children who recovered. A dermatosis of the chronic type, consisting of "burnished," "crackled,"

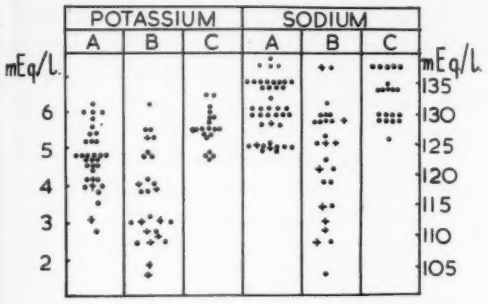

Fig. 2. Serum potassium and sodium values in 3 groups of children: *A*, patients without evidence of dehydration; *B*, patients with clinical evidence of dehydration; *C*, normal controls. Fatalities are represented by crosses.

TABLE I

Incidence of Dehydration and Nutritional Edema in 100 Malnourished African Children

Condition of patient	No. edematous	No. nonedematous	Total no. patients
Clinically dehydrated	25 (8)[a]	10 (5)	35 (13)
Not dehydrated	57 (5)	1 (0)	58 (5)
State of hydration uncertain	7 (2)	—	7 (2)
TOTAL	89 (15)	11 (5)	100 (20)

[a] Numbers in parentheses are fatal cases.

"mosaic," and "sooty" skin areas,[4] was present in 3 (15 per cent) of the fatal cases and in 30 (38 per cent) of the survivors, and therefore its presence did not influence the prognosis adversely. Two (10 per cent) of the fatal cases and 12 (15 per cent) of the surviving cases showed no evidence of a dermatosis.

Edema, Clinical Dehydration, and Abnormal Electrolyte Levels

The influence of nutritional edema and clinical dehydration on the mortality is shown in Table I. Of 57 children who were edematous, but showed no evidence of dehydration, only 5 (8.8 per cent) died. Edema was associated with dehydration in 25 patients, and 8 (32 per cent) of these died.

In 7 patients, of whom 2 died, extreme wasting and loss of subcutaneous fat made it impossible to assess the clinical state of hydration by skin elasticity. Among the remaining 93 children, there were 35 with varying degrees of dehydration, and 13 (37 per cent) of these died. In 58 patients, clinical dehydration could not be detected, and of these only 5 (9 per cent) died.

Low serum sodium and potassium levels were common in dehydrated patients (Fig. 2) and were associated with a high mortality, despite intravenous replacement therapy.

Liver Enlargement

An enlargement of the liver to $1^1/_2$ inches (2 fingerbreadths) or more below the costal margin in the right midclavicular line was more common in children who succumbed to the disease: it was found in 9 (45 per cent) of the fatal cases and in only 11 (14 per cent) of the survivors. Postmortem examinations were carried out on only 2 of these cases, and both had grossly fatty livers which resembled putty in color and consistency.

Hypothermia

A body temperature below 95°F was a grave prognostic sign. Two patients arrived at the hospital with temperatures of 87°F and 87.7°F, respectively, and both died within a few hours. Three others developed hypothermia in the hospital. Of these, 2 died and 1 recovered after the temperature had fallen to 88.8°F. Serum potassium levels were investigated in only 3 of the hypothermic children and were found to be 3.2, 2.9, and 2.6 meq/l, respectively.

Clouding of Consciousness

Occasionally death was preceded by drowsiness or sudden stupor. In one such case in this series, the blood sugar level was 13 mg/100 ml shortly before death, and in another fatal case a level of 44 mg/100 ml was obtained.

Infection

The death rate was not influenced by the presence of certain infections. *Shigella* organisms were isolated from 10 children, with only one death, and *Salmonella* organisms were found in 5 children, all of whom survived. Active pulmonary tuberculosis was encountered in 10 children. One of these, a child with severe tuberculous bronchopneumonia, died

within a few hours of arrival at the hospital. The remaining 9 patients survived.

DISCUSSION

This survey has shown that, with the therapy in current use at this hospital, the prognosis in protein malnutrition is grave in the presence of one or more of the following signs: severe wasting, acute dermatosis, dehydration and low sodium and potassium levels, marked enlargement of the liver, and hypothermia. Drowsiness and stupor may indicate hypoglycemic attacks which are commonly fatal.

No prognostic significance could be attached to age, retardation of growth, chronic dermatosis, and associated shigellosis, salmonellosis, or pulmonary tuberculosis.

The "atrophic" type of malnutrition was stated by Altmann[7] to have a serious prognosis, and this was confirmed in the present investigation. Starvation is known to be fatal in many adults when 50 per cent of the initial body weight has been lost, and the greatest weight loss recorded in a mammal was in a dog which had lost 65 per cent of its initial body weight at death.[8]

An acute nutritional dermatosis is always an indication of an advanced degree of protein malnutrition.[4] In this part of Africa such skin lesions are found exclusively in patients who have been consuming a faulty diet containing mainly maize, the local staple food. We have of late treated these patients with plasma infusions, and the results appear to be favorable. The acute dermatosis is not seen in children who develop protein malnutrition while subsisting on a diet of wheat products or oatmeal. In the absence of a nutritional dermatosis the prognosis is better, a fact observed previously by Altmann.[7]

Despite the fact that the water content of the skin of malnourished dehydrated patients is higher than that of normal controls,[9] it is useful to retain the concept of "dehydration" in clinical practice. In this series, evidence of clinical dehydration was commonly associated with marked lowering of the serum electrolyte levels. Furthermore, the mortality of the dehydrated children was nearly 40 per cent, and thus 4 times higher than the death rate of well-nourished dehydrated children at this hospital. It has been stated that the unsatisfactory response of malnourished dehydrated children to intravenous fluid therapy is due to renal dysfunction.[10]

Hypothermia revealed itself as a highly fatal complication of protein malnutrition. It is not caused by climatic conditions. It is often a manifestation of severe hypopotassemia, which causes muscular atony or paralysis, resulting in impaired production of body heat.

Marked enlargement of the liver was much more common in fatal cases, an observation already made by Altmann.[7] Parasitic infestations, which could cause such enlargement, are extremely rare in this part of Africa. At autopsy the enlarged liver is usually found to be the seat of extensive fatty changes. Unexpected death, preceded by a brief period of stupor, is particularly common in this type of patient. In one case included in this series, and in a number of others,[11] we have been able to prove that this mode of death, with which other workers are well acquainted,[4a] is due to severe hypoglycemia.

SUMMARY

Observations on 100 children with manifestations of severe protein malnutrition show that a fatal outcome is more likely in the presence of one or more of the following factors: (1) advanced emaciation, in this instance a body weight 50 per cent or more below average; (2) acute nutritional dermatosis; (3) clinically detectable dehydration, which in the patients in this series was often associated with markedly lowered serum sodium and potassium levels; (4) marked enlargement of the liver; and (5) hypothermia.

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Relation of Age and Body Weight to the Frequency of Local Tissue Changes Suggestive of Malnutrition

The Five-Year Experience of a District Health Center Nutrition Clinic in New York City

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THE clinical appraisal of nutriture includes, besides the measurement of readily quantitated parameters such as height, weight, and skin folds, the identification of selected qualitative tissues changes commonly associated with an impaired nutritional state. Although these physical signs are no longer regarded as conclusive evidence of specific deficiencies, or—except perhaps for the target tissue itself—even of malnutrition, the occurrence of certain of these lesions is accorded significance in many examination routines.[1–9]

The frequency with which these tissue changes are noted, particularly in epithelial components of skin and mucous membranes, is inevitably a function of the population investigated.[10–28] Various estimates suggest a high prevalence among obviously malnourished groups;[12–14, 19–22, 26] they are even found, albeit to a lesser degree, in ostensibly healthy persons.[2–4, 8, 10, 17, 18, 27] Only limited data are available to indicate the extent to which the occurrence of these lesions within a given population appears to be influenced by such factors as race, sex, age, and body weight.[11, 14, 16, 19–25] The present report endeavors to evaluate apparent relationships between age and relative body weight and the prevalence of a group of selected qualitative tissue changes commonly identified as signs of malnutrition.

MATERIAL AND METHODS

The material represents one phase of an analysis of the initial five-year experience of a New York City Health Department nutrition clinic.† From 1949 to 1954, 3,500 individual patients were studied, of whom records were subsequently available on 3,459. Of these, 22 were excluded by reason of incomplete information, chiefly because of failure to permit a complete examination. A total of 708 prenatal patients will be considered in a separate report,‡ leaving 2,729 subjects in the present study. The group included 2,076 (75 per cent) white, 307 (11 per cent) Negro, and 328 (13 per cent) Puerto Rican patients, in addition to 18 (1 per cent) of nonidentified ancestry. There were 758 males and 1,971 females, varying in age from less than 1 to more than 70 years. A

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‡ The relation of factors of race and sex to the occurrence of local tissue changes will be analyzed in a subsequent report, incorporating observations on the prenatal group.

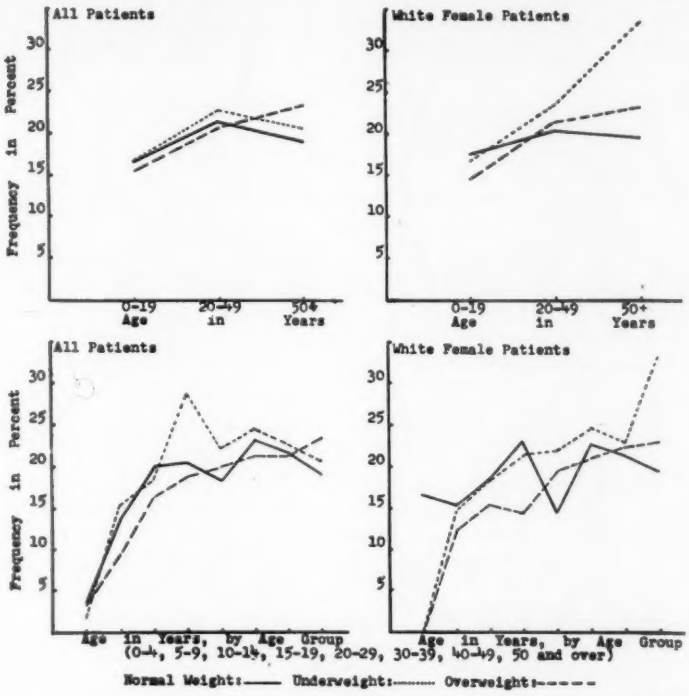

Fig. 1. Frequency of selected tissue changes in a nutrition clinic population (2,729 patients, including 1,497 white females), by age and relative body weight. Average of 12 lesions.

total of 1,788 were below 20, 714 between 20 and 49, and 227 over 50 years.

Because of the uneven distribution of the sexes and of the three principal ethnic groups among the different age groups represented, the factors of age and sex were not evaluated in the present study.* To delineate the influence of weight and age independent of effects of sex and race, a separate analysis was made of lesion frequencies in the largest clinic subgroup—1,497 white females, representing 54.9 per cent of the total patients considered.

Patients were classified as normal, underweight, or overweight according to tables adapted from Baldwin[30] for young children, from Faber[29] for older children, and from Jolliffe[31] for adults. Interpretation was conservative, so that individuals identified as normal doubtless included many who would be regarded as overweight or underweight by other criteria; however, those listed as overweight or underweight were all but certainly in the correct groups. Subjective clinical impressions, which commonly permit inadequate distinction between overweight and obesity, and between underweight and undernutrition, were not involved in the present classification, although generally good agreement was evident.

The qualitative tissue changes selected for specific evaluation from among those routinely recorded in the clinic were: acne vulgaris, acne rosacea; follicular hyperkeratosis; xerosis, conjunctival thickening, marginal blepharitis; dyssebacea; cheilosis; angular stomatitis; glossitis; fissuring of the tongue; and gingivitis. Criteria for the diagnosis of these lesions were those in use by the Bureau of Nutrition, substantially in accordance with Jolliffe, Tisdall, and Cannon.[3] Lesions were identified only as present or absent without regard to factors of intensity, severity, duration, or

* See last footnote, p. 166.

TABLE I

Frequency of Blood Hemoglobin Levels and Selected Tissue Changes in a Nutrition Clinic Population

By relative body weight

Weight status	No. patients	Hemoglobin (g)[a]				Individual tissue "change"												
		<7.5	7.5–10.0	10.0–12.4	>12.4	Acne vulg.	Acne ros.	Follic. hyper-ker.	Xerosis	Conjunc. thick.	Marg. bleph.	Dysse-bacea	Cheilo-sis	Angular stomat.	Glos-sitis	Tongue fissures	Gingi-vitis	Average all lesions
Normal	622	0.2	2.6	43.9	53.3	12.7	0.2	35.5	18.2	10.5	13.0	2.3	29.7	5.8	27.3	20.4	35.9	17.8
Underweight	665	0	3.5	44.0	52.6	14.1	0.3	35.8	23.3	11.1	14.6	2.6	34.6	2.9	24.2	13.8	34.4	17.7
Overweight	1411	0	1.0	27.1	71.9	21.9	1.2	33.9	17.4	18.7	5.3	2.9	17.0	2.4	31.6	22.3	43.4	18.2
Unknown	31	0	12.5	62.5	25.0	12.9	0	35.5	51.6	12.9	3.2	0	35.5	0	96.8	9.7	38.7	22.0
TOTALS	2729	0.1	2.0	35.3	62.6	17.8	0.7	34.8	19.4	14.8	9.3	2.6	24.4	3.4	29.6	19.7	39.4	18.0

[a] Hemoglobin determinations on 2,692 patients.

TABLE II

Frequency of Blood Hemoglobin Levels and Selected Tissue Changes in a Nutrition Clinic Population

White females, by relative body weight

Weight status	No. patients	Hemoglobin (g)[a]				Individual tissue "change"												
		<7.5	7.5–10.0	10.0–12.4	>12.4	Acne vulg.	Acne ros.	Follic. hyper-ker.	Xerosis	Conjunc. thick.	Marg. bleph.	Dysse-bacea	Cheilo-sis	Angular stomat.	Glos-sitis	Tongue fissures	Gingi-vitis	Average all lesions
Normal	285	0	1.4	39.4	59.2	18.2	0.4	33.3	21.4	11.6	12.3	4.2	23.2	2.5	32.3	30.5	37.9	19.0
Underweight	262	0	1.2	37.6	61.2	20.6	0.8	33.2	19.8	7.6	18.3	4.6	29.0	3.8	31.7	15.3	36.3	18.4
Overweight	941	0	0.2	25.5	74.3	19.4	1.6	30.1	17.9	18.7	6.4	3.3	15.2	3.3	36.6	26.7	45.8	18.7
Unknown	9	0	0	50.0	50.0	22.2	0	55.6	22.2	33.3	0	0	55.6	0	33.3	22.2	55.6	25.5
TOTALS	1497	0	0.6	30.4	69.0	19.4	1.2	31.4	18.9	15.6	9.6	3.8	19.4	3.1	34.9	25.4	42.7	18.8

[a] Hemoglobin determinations on 1,486 patients.

etiology. All data were derived from the initial clinic examination only. Changes observed on subsequent visits, often over a few years, were not considered in the present study.

RESULTS

Results are summarized and statistically evaluated in the accompanying tables and figures.

Table I and Figures 1 and 2 indicate the findings in the total group of patients selected for analysis. The frequency of tissue changes appears significantly related to both age and relative body weight, although their over-all prevalence seems more related to age. In general, the number of total lesions increases with age in all weight groups, although underweights exhibit a maximum frequency at 15–19 years.

Individual lesions necessarily parallel total tissues changes observed in respect to age, although noteworthy exceptions apparently occur (see Fig. 2). Acne vulgaris is most common in the 15–19-year group, and follicular hyperkeratosis in the 10–14-year group, following which both decrease with age. Cheilosis shows a bimodal frequency distribution, with both early and late peaks in incidence. Marginal blepharitis and angular stomatitis show no apparent variation with age.

Although total lesion frequency, hence most individual lesion frequencies, shows less influence of relative body weight, some variations among the three major weight groups are seen, especially in respect to those lesions seemingly least affected by age. Marginal blepharitis and cheilosis, for example, are more common among underweights, and active angular stomatitis occurs most frequently in the normal weight group. In some instances, relationships of tissue changes to relative body weight appear to vary with age. Acne vulgaris occurs more frequently among overweights in the pubescent group and among underweights in the postpubescent group.

Table II and Figures 1 and 3 indicate the findings in the group of 1,497 white female patients. In general, these are similar to the over-all patient experience; age seems a more important factor than relative body weight, although the maximum frequency of total lesions occurs in later years. Some of the relationships noted in the total group are more evident in this partial sample, where variables relating to race and sex are not involved. The relatively greater frequency of acne vulgaris in the overweight children before puberty and in the underweight children after puberty (inferred from age) is accentuated. Comparable associations are observed in respect to the occurrence of glossitis and, to a lesser degree, of follicular hyperkeratosis.

Impressions concerning the occurrence of the individual tissue changes, derived specifically from the white female subsample (see Table II, and Fig. 2), are summarized as follows, with lesions in order of relative frequency:

(1) *Gingivitis.* Gingivitis occurred in 42.7 per cent, with an early rapid increment with age. There was no consistent relation to body weight.

(2) *Glossitis.* Glossitis occurred in 34.9 per cent, with a gradual increase with age. There was no apparent relation to body weight.

(3) *Follicular Hyperkeratosis.* Follicular hyperkeratosis occurred in 31.4 per cent, with a progressive increase in prevalence to a sustained plateau in older groups. The peak was earlier among overweights.

(4) *Fissuring of Tongue.* Fissures of the tongue occurred in 25.4 per cent, with a gradual increase with age. There was no consistent relation to weight, but an earlier increment was noted in underweights.

(5) *Acne Vulgaris.* Acne vulgaris occurred in 19.4 per cent, with its peak in the 15–19 and 20–29-year age groups. The peak was earlier in overweights.

(6) *Cheilosis.* Cheilosis occurred in 19.4 per cent, with an early increment with age to a relative plateau. It was most frequent in underweights.

(7) *Xerosis.* Xerosis occurred in 18.9 per cent, with a gradual increment with age. It was more frequent in underweights.

(8) *Conjunctival Thickening.* Thickening of the conjunctivae occurred in 15.6 per cent, with no consistent relationship to age. It was most frequent in underweights.

(9) *Marginal Blepharitis.* Marginal blepharitis occurred in 9.6 per cent, being more common in younger groups, especially underweights.

(10) *Dyssebacea.* Dyssebacea occurred in 3.8 per cent, with no consistent relationship to age or body weight.

(11) *Angular Stomatitis.* Angular stomatitis occurred in 3.1 per cent, with a gradual increase with age. There was no apparent relation to weight.

(12) *Acne Rosacea.* Acne rosacea occurred in 1.2 per cent, most commonly in the older age groups, but with no apparent relation to body weight.

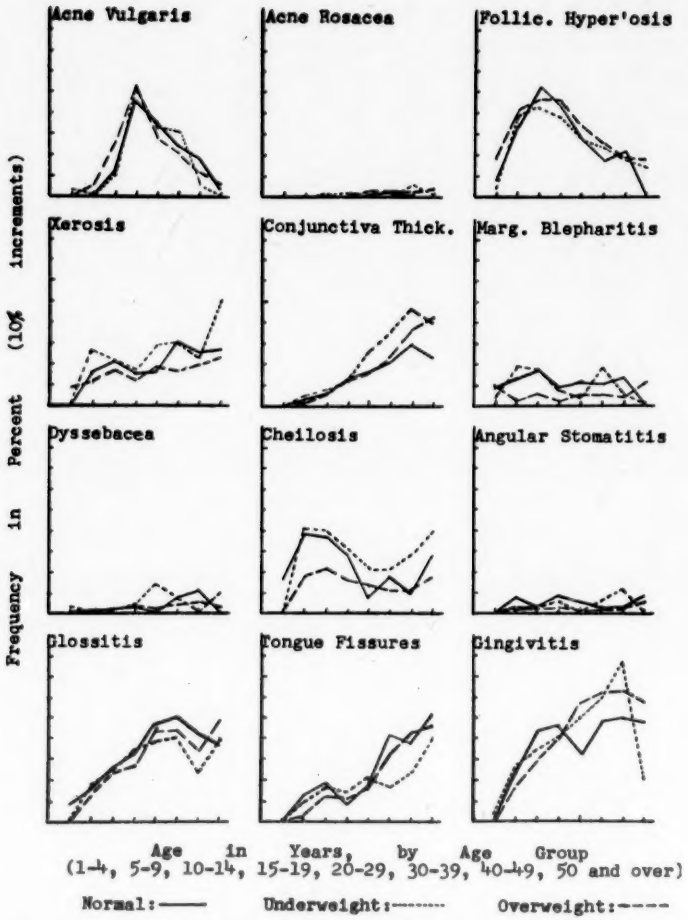

Fig. 2. Frequency of individual tissue changes in a nutrition clinical population (2,729 patients), by age and relative body weight.

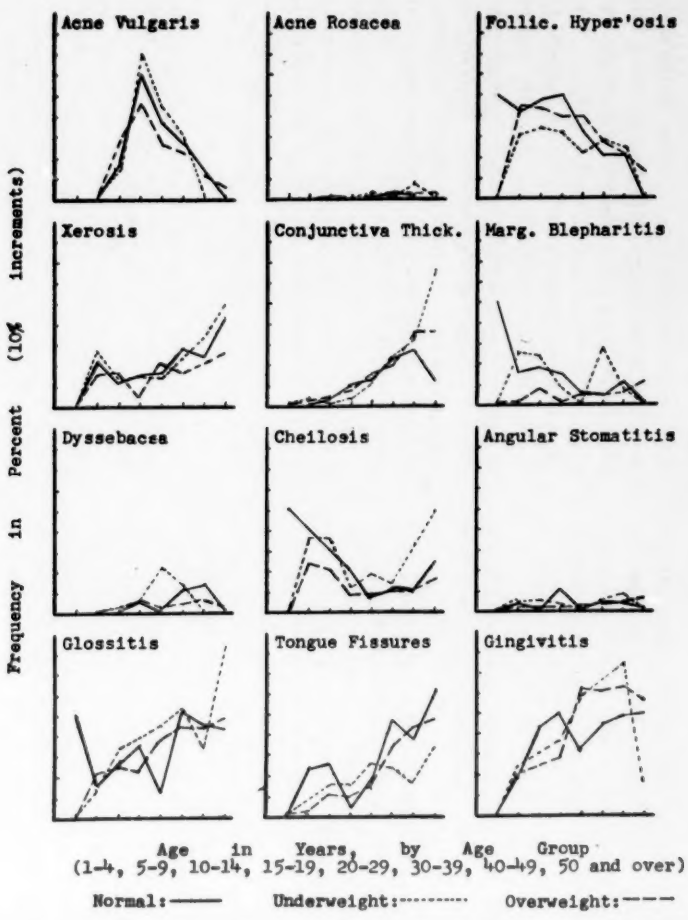

Fig. 3. Frequency of individual tissue changes in a nutrition clinic population, 1,497 white females, by age and relative body weight.

TABLE III

Statistical Evaluation of Differences in Frequency of Selected Tissue Changes in Patients in Different Age and Weight Groups

Tissue change	Age group	Weight group	Probability	
			All patients	White female patients
Total changes	All Ages	NW: UW: OW[a]	>.90	>.90
Acne vulgaris	All Ages	NW: UW: OW[a]	<.001	>.70
Acne rosacea	All Ages	NW: UW: OW[a]	<.05	>.30
Follic. hyperkerat.	All Ages	NW: UW: OW[a]	>.50	>.30
Xerosis	All Ages	NW: UW: OW[a]	<.01	>.30
Conjunc. thick.	All Ages	NW: UW: OW[a]	<.001	<.001
Marg. blepharitis	All Ages	NW: UW: OW[a]	<.001	<.001
Dyssebacea	All Ages	NW: UW: OW[a]	>.50	>.30
Cheilosis	All Ages	NW: UW: OW[a]	<.001	<.001
Angular stomatitis	All Ages	NW: UW: OW[a]	<.01	>.50
Glossitis	All Ages	NW: UW: OW[a]	<.001	>.20
Tongue fissures	All Ages	NW: UW: OW[a]	<.001	<.001
Gingivitis	All Ages	NW: UW: OW[a]	<.001	<.01
TOTAL CHANGES	All Ages	UW: OW[a]	>.83	>.91
	0–19; 20–49; 50+[a]	All Weights	<.01	<.01
	0–19	UW: OW[a]	>.04	>.40
	20–49	UW: OW[a]	>.65	>.70
	50+	UW: OW[a]	>.80	>.65

N = normal weight; O = overweight; U = underweight.

[a] Denotes groups compared.

Statistical evaluations of some of these observations are summarized in Tables III and IV. Differences between different age groups are statistically significant ($P < 0.05$) in respect to both total lesion frequency and certain individual lesion occurrence. However, differences between weight groups are not significant in respect to total lesions, probably because of opposing distributions of individual tissue changes.

Parenthetically, an observation not readily subject to quantitative documentation indicates that excessive length of eyelashes is frequently encountered among overweight as well as underweight (in contradistinction to normal weight) patients. Relative hirsutism, notably of the extremities, also seems more common among underweight individuals with poor muscle development, especially among prepubescent females of all ethnic groups.

COMMENT

The limitations of the present study are readily apparent. Chief among these is the nonrandom composition of the study sample. A majority of patients were referred to the clinic for self-diagnosed weight problems and/or of symptomatology thought possibly attributable to faulty diet. Findings cannot, therefore, be construed as necessarily representative of the general population.

Failure to take into account the severity of tissue changes justifies concern for the equal weight accorded each observation of a given lesion. Validity is further compromised by the arbitrary device of equating, in total frequency counts, all changes observed, irrespective of tissue affected.

Variations in diagnostic criteria among examining physicians represent a further element of bias, to be analyzed in a subsequent report. However, 83.8 per cent of all examinations were performed by three of approximately 12 physicians, among whom essentially equal patient group distribution may reasonably be presumed.

The generally greater prevalence of these tissue changes in older age groups suggests a "causal" relationship, analogous perhaps to the increased frequency of arteriosclerosis with ad-

TABLE IV
Statistical Evaluation of Differences in Frequency of Selected Tissue Changes in Patients in Different Age and Weight Groups

White females

Change	Age group(s)	Weight group(s)	Probability
Acne vulgaris	0–19; 20–49; 50+[a]	OW	<.001
	0–19	UW: OW[a]	<.05
	20–49	UW: OW[a]	<.05
	10–14	UW: OW[a]	<.03
	15–19	UW: OW[a]	<.02
Acne rosacea	0–19; 20–49; 50+[a]	OW	<.05
Follic. hyperkerat.	0–19; 20–49; 50+[a]	NW	<.001
	0–19; 20–49; 50+[a]	OW	<.001
Xerosis	0–19; 20–49; 50+[a]	OW	<.01
Marg. blepharitis	0–19; 20–49; 50+[a]	OW	>.05
	0–19; 20–49[a]	NW	<.01
	0–19; 20–49[a]	UW	>.10
	20–49	UW: OW[a]	<.001
	0–19	UW: OW[a]	<.001
	5–9	UW: OW[a]	<.001
	15–19	UW: OW[a]	<.02
	20–29	UW. OW[a]	>.07
Cheilosis	0–19; 20–49; 50+[a]	OW	.01
	0–19	NW: UW: OW[a]	<.001
	20–29	NW: UW: OW[a]	>.05
	0–19; 20–49[a]	NW	<.001
	0–19; 20–49[a]	UW	>.08
Angular stomatitis	0–19; 20–49; 50+[a]	OW	<.01
Glossitis	0–19; 20–49; 50+[a]	OW	<.001
	0–19; 20–49[a]	NW	<.01
	0–19; 20–49[a]	UW	<.03
Tongue fissuring	0–19; 20–49; 50+[a]	OW	<.001
	0–19; 20–49[a]	NW	<.01
	0–19; 20–49[a]	UW	>.07
Gingivitis	0–19; 20–49; 50+[a]	OW	<.001
	0–19; 20–49[a]	NW	>.27
	0–19; 20–49[a]	UW	<.001

N = normal weight; O = overweight; U = underweight.

Comparisons of three major age groups involve principally overweight patients, for reason of small numbers of normals and underweights in groups over 50 years.

[a] Denotes groups compared.

[b] Lesions show greater frequency in overweights in younger subgroup and greater frequency in underweights in older subgroups.

vancing years. However, since no distinction was made here between either acute and chronic, or between mild and severe, changes, some lesions, notably fissuring of the tongue and gingival changes as in healed cracks at the angles of the mouth, may frequently represent "scars" of previous malnutrition rather than currently active processes. Moreover, while fissuring of the tongue is thought frequently to be a familial, often a congenital, lesion, its significantly greater occurrence in the older age group appears to indicate an acquired development, at least in many instances. A constitutional predisposition must, of course, be operative in the appearance of this, as well as other lesions, to be manifested only under conducive environmental conditions.

The association of tissue changes with dif-

ferences in body weight appears real, but is difficult to interpret. The almost identical frequencies of some lesions in normal, under-, and overweight groups, especially of the same age, warrant the speculation that similar frequencies might be demonstrated among the general population, indicating compatibility with ostensibly satisfactory (at least when weight is the index) states of nutrition. The nonspecificity of these lesions has been alluded to. A satisfactory definition of normal—as distinct from usual or common—occurrence is germane,[7] but not essential, to the present study, which seeks only to evaluate frequencies of tissue changes among different groups within a special clinic population.

The concept that overnutrition, like undernutrition, is a form of malnutrition may gain support from the often comparable frequencies of tissue changes in both groups. The so-called normal weight individuals, themselves also largely referred because of suspected malnutrition and including large numbers who would be classified as underweight by less conservative criteria, assuredly cannot be accepted as a satisfactory control group. The observation that the generally "better" nourished (calorically), overweight patients commonly showed lesion frequencies comparable to those noted in the underweights is consistent with the hypothesis that hypoalimentation is protective against, while rapid growth is conducive to, the development of deficiencies. The earlier increments in acne vulgaris (also noted by Jolliffe *et al.* in Cuban children[28]), glossitis, and follicular hyperkeratosis among overweights suggest the influence of a frequently noted earlier maturation of individuals in this category.

The practical implications of this analysis are largely speculative. While lacking the conclusiveness of studies on random segments of the general population, or of ideal (if unrealistic) longitudinal studies of a large representative group, the present findings nevertheless indicate the occurrence of local tissue changes to be in part a function of age and body weight or of some common denominator. In the interpretation of apparent lesions, physicians would seem increasingly obligated to consider these as well as other patient attributes, and to review regularly their personal concepts of, and clinical criteria for evaluation of, the nutritional state.

SUMMARY

The prevalence of twelve selective qualitative tissue changes commonly associated with malnutrition was determined in 2,729 patients examined over a five-year period in a New York City Health Department nutrition clinic. Observations in a subgroup of 1,497 (54.9 per cent) white females were analyzed separately to provide impressions concerning apparent effects of age and relative body weight, independent of factors of sex and race.

The frequency of tissue changes appeared significantly related to age and, to a lesser extent, to relative body weight. Individual tissue changes showed significant differences from the frequency pattern for all tissue changes. In general, the number of total lesions increased with age in all weight groups, although underweights exhibited a peak frequency at 15–19 years of age. The influence of relative body weight seemed greatest in respect to tissue changes least affected by age.

ACKNOWLEDGMENT

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Food Intake and Weight Changes of Youths on an Exploring Expedition

A. M. W. PORTER, M.B., B.S.*

IN THE summer of 1956 an expedition of the British Schools Exploring Society, consisting of 9 leaders and 50 boys, spent six weeks in central Iceland. The purpose of these annual expeditions is to provide selected schoolboys with a training in self-reliance and leadership, and with a chance to participate in scientific work in the field.

The opportunity was taken during the 1956 expedition to record frequent weighings on the 50 schoolboys. The resulting data yield information on the calorie intake required by youths doing hard work in a cool climate.

EXPERIMENTAL

Environment

The base camp was situated near Langjokull glacier in the middle of a large lava plain; this region is intersected by fast-flowing and ice-cold glacial rivers. Every member lived under canvas throughout the expedition, and all tents, food, etc., were carried in packs on the back. The summer of 1956 was a relatively fine one, and the temperature rarely fell below freezing except on the glacier. Table I shows the mean weekly maximum and minimum temperatures at the base camp.

Type of Work

The 50 boys may be conveniently divided into two groups. The first consisted of 28 "marchers," who worked hard but intermittently; a day's march entailed carrying a pack of 15 to 30 kg for a distance varying from 15 to 30 km at a speed of about 5 km per hour. The duration of the marches ranged from 5 to 15 days; the total number of days spent marching by each boy in this group averaged 19 but varied widely, depending on the length of the interludes in base camp.

The second group comprised 20 "surveyors," whose work was more continuous but less strenuous than that of the "marchers" and was estimated as being equivalent to marching about 13 km a day with a 5 kg pack. The remaining two boys sustained injuries and spent the greater part of the expedition in base camp.

Diet

The daily ration for each subject weighed 30 ounces; its composition was originally fixed by the late Surgeon Commander Murray Levick on the basis of his antarctic experiences, and was composed by weight of 61 per cent carbohydrate, 20 per cent fat, and 19 per cent protein. The standard daily ration in oz/man/day was: biscuits 12, pemmican 2, cheese 4, margarine 2, sugar 2, dried vegetables 2.5, chocolate 2, oatmeal 2, raisins 1, salt 0.25, tea 0.25, and one tablet of ascorbic acid (50 mg). This ration was reputed to provide 3,638 calories a day. Although the original method of calculation is not clear, this figure agrees closely with one derived from the tables of McCance and Widdowson;[4] occasional supplements in base camp increased the over-all mean daily intake to about 3,670 calories a day.

The rations proved acceptable to all, there was no plate waste, and opportunities for unofficial supplementation were rare; it would be reasonable therefore to conclude that a fixed calorie intake applied to all members.

Method of Weighing

A steelyard scale, calibrated to quarter

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TABLE I

Mean Weekly Maximum and Minimum Temperatures at Base Camp

Period	Temperature (°F) Maximum	Minimum
Aug. 6–12	54.5	38.8
13–19	58.9	40.9
20–26	52.6	38.8
Aug. 27–Sept. 2	52.0	32.7
Sept. 3– 9	52.9	41.1
10–11	45.9	32.1

kilograms, was suspended from metal struts and the subject to be weighed sat in a boatswain's chair of known weight. The whole apparatus was surrounded by a windbreak of canvas in order to avoid swaying.

Unfortunately it did not prove practical to check the absolute accuracy of the scale, but its type and simplicity excluded the possibility of any gross error; moreover, for the purposes of the investigation, the absolute accuracy of the scale was of less importance than its consistency in measuring *change* of weight. Two observers only were concerned with all the weighings throughout the expedition, and when they both on the same occasion repeatedly, but independently, weighed a group, it was found that the range of variation of the readings did not exceed 0.5 kg for any one subject.

Each person, wearing underwear only, was weighed as opportunity offered at approximately weekly intervals; every effort was made to weigh a "marcher" immediately before and after a march. The frequent weighing in the field of so many subjects made it difficult to standardize conditions, such as the time of the day in relationship to meals, but errors of o.5 kg or more were probably rare.

RESULTS

In Table II will be found the mean and standard deviations of the ages, heights, and initial body weights of the 50 subjects.

Changes in Body Weight

The "Marchers:" Examination of the weight charts of the subjects in this group shows that their body weights responded to the different phases of the expedition in a similar and consistent manner, permitting the following generalizations: (1) During the intervals between marches there occurred either a check in the rate of loss of weight or an actual regaining of weight. (2) While on the march there was a loss of weight or a decrease in the previous rate of gain. (3) During the period immediately following the end of the expedition there was a rapid regaining of weight.

TABLE II

Mean and Standard Deviations of the Ages, Heights, and Initial Body Weights of the 50 Subjects

	Mean	Stnd. Dev.
Age	18.1 years	0.7
Initial body weight	64.0 kg	6.6
Height	177 cm	6.0

Figure 1 shows an actual weight chart which illustrates these points, and in Table III may be found the frequency of different rates of weight change in relation to the number of marches. It will be seen that the most frequent rates of weight change were losses of 0.1 and 0.2 kg a day.

Whether a "marcher" had an over-all gain or loss of weight during the expedition depended largely on the total number of days he spent marching. Of those who were out for more than half of the six weeks, 10 out of 15 lost weight, the mean loss being 1.3 kg and the maximum 5.0 kg. The remaining 13 subjects, who were out for less than half the time, had

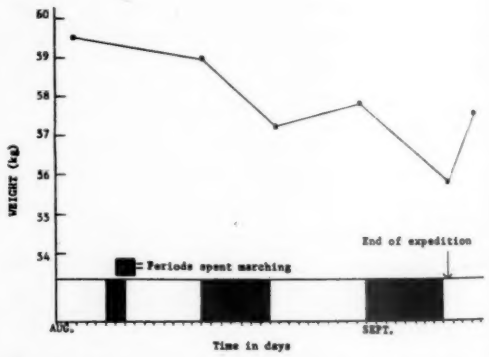

Fig. 1. The body weight chart of a "marcher," demonstrating typical fluctuations during the expedition.

TABLE III

Frequency of Different Rates of Weight Change in Relation to Number of Marches (Total of 41 Marches by 28 Boys)

No. marches	Weight change (kg/day)
1	+0.2
1	+0.1
7	0.0
13	−0.1
12	−0.2
6	−0.3
1	−0.4

a mean gain of 1.4 kg, and only one lost weight.

The "Surveyors:" The body weights of the subjects in this group showed only minor fluctuations, and the majority finished the expedition at the same weight as they started; in contrast, the two boys confined to base camp finished 4.0 kg and 2.5 kg heavier than their initial weight.

Rate of Regaining Weight: Unfortunately it was possible to follow up the weights for only two days after the end of the expedition. During this short time, when virtually unlimited food was available, a rapid and universal increase in weight was demonstrated. The "marchers" regained a mean of 1.7 kg and the "surveyors" a mean of 1.2 kg; 12 boys, of whom 9 had been "marchers," regained as much as 2.5–3.0 kg.

DISCUSSION

The 50 subjects of this investigation were all volunteers selected by an interviewing committee from 350 applicants and were drawn for the most part from British public and grammar schools.

It will be shown in another paper that their physiques or somatotypes differed from those of a control group of public-school boys. The "explorers" had a significantly lower rating in endomorphy and a higher one in ectomorphy (Sheldon's classification[8]); it is very unlikely that this difference was due to a bias on the part of the selection committee. Such an expedition seems, therefore, to have a particular appeal for the leaner members of the schoolboy community. Hehir[3] noted that during the siege of Kuts loss of weight was maximal in those who began the siege with a superabundance of fat. It is probable, therefore, that any weight losses recorded for our predominantly ectomorphic subjects were minimal and might well have been greater if the group had not differed from the general population in respect to physique.

From the information provided by Passmore and Durnin[6] in their review of the literature pertaining to human energy expenditure, it can be deduced that a man carrying a load of 21 kg at a speed of 5 km an hour over a smooth surface expends energy at a rate of about 5 cal/min. In view of the very rough surface of the block lava and boulders, the "marchers" probably exceeded this figure, their energy expenditure being comparable to such heavy tasks as drilling coal (5.8 cal/min) and sawing softwood (6.3 cal/min). The work expended by a subject during a march must, therefore, be rated as high, for in addition to carrying a heavy pack across country for up to seven hours a day, there were the everyday chores of life to perform, such as pitching camp, fetching water, and cooking. The importance of this "nonoccupational" type of activity in influencing calorie requirements has been pointed out by the Food and Agricultural Committee of the United Nations;[2] this committee also estimated the calorie intake of youths in a normal state of health and activity to be 3,800 cal/day. Widdowson, Edholm, and McCance[9] showed that the energy expenditure of cadets at a military establishment was about 3,420 cal/day and that, contrary to expectation, the cadets were not leading lives of intense activity, much of the day being devoted to sedentary occupations.

It might therefore be anticipated that our subjects would lose weight while marching on an intake of about 3,640 cal/day, and in fact a loss of between 0.1 and 0.2 kg/day was demonstrated for the majority. It can be deduced from information provided by Morgulis,[5] about a group of fasters, that the initial rate of weight loss in complete starvation is

about 0.9 kg/day. Thus the rate of loss of weight of the "marchers" was not excessive, but it does nonetheless provide a clear indication that the daily calorie intake was insufficient for their energy demands. Further support for this conclusion is provided by the fact that, after an initial latent period, the majority of "marchers" became very hungry and remained so for the rest of the expedition.

It is possible that a small proportion of the body weight loss occurring while on the march was due to a temporary state of dehydration, which only slowly corrected itself on return to base camp and consequently influenced the readings. However, there was no "clinical" evidence to support this, and ample fluids were usually readily available.

The 20 subjects in the survey group seemed to find the rations more satisfying than the "marchers," and it has already been noted that their body weights did not alter appreciably throughout the expedition.

Although the maintenance of a steady body weight by adults may be taken to indicate that they are receiving an adequate calorie intake, no such assumption can be made for a group of youths who are still close in time to the adolescent growth spurt and have recently exchanged a relatively sedentary life for one of hard work and exertion. It must be suspected that if the rations had been entirely adequate for the needs of the "surveyors," a trend to gain weight, such as Rosenbaum[7] demonstrated for British army recruits following "call-up," would have occurred; no such trend was discernible.

The conclusion that the mean daily intake of 3,670 calories was not quite sufficient for the subjects in this group is supported by the behavior of their body weights at the end of the expedition, for Benedict *et al.*[1] showed that a rapid regaining of weight occurs at the termination of a period of reduced diet.

In view of the above findings the Society implemented a scheme to provide an increased ration scale for the 1957 expedition.

SUMMARY

The opportunity was taken during an expedition to central Iceland to record at frequent intervals the body weights of the 50 schoolboy members. These subjects could be divided into two groups: 28 "marchers" who worked hard but intermittently, and 20 "surveyors" whose task was less strenuous but more continuous.

The ration scale provided an intake of about 3,640 cal/day for all the subjects; at base camp the rations were occasionally supplemented to increase the over-all mean intake to about 3,670 cal/day.

The majority of subjects lost weight while out on a march; the most frequent rates of loss were 0.1 and 0.2 kg/day. Only minor fluctuations occurred in the body weights of the "surveyors."

It is concluded that the ration scale was inadequate for the "marchers" and of doubtful adequacy for the "surveyors."

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Growth and Development of Central American Children

II. The Effect of Oral Administration of Vitamin B_{12} to Rural Children of Preschool and School Age

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THE DISCOVERY of vitamin B_{12} and its stimulatory effect on the growth of experimental animals under certain conditions soon led to studies of its influence on the growth of children, particularly on those whose development appeared to be retarded. Unfortunately, these studies have frequently yielded quite conflicting or inconclusive results, as recently reviewed by Howe.[1]

The first report[2] on the administration of vitamin B_{12} introduced an experimental design and statistical procedures which are still controversial. In this study the authors concluded that 5 of 11 children responded in a dramatic and highly significant manner. This has been followed by the inconclusive results of Chow[3,4] and reports of suggestive positive effects on at least some children by O'Neil and Lombardo,[5] Bidault,[6] Wetzel *et al.*,[7] Wilde,[8] Jolliffe and his associates,[9] Larcomb and collaborators,[10] Crump and Tully,[11] and Grüninger and coworkers.[12] Negative reports also appeared beginning with Benjamin and Pirrie[13] and Spies and his associates.[14] The papers of Scrimshaw and Guzmán,[15] Someswara Rao *et al.*,[16] and Mackay *et al.*,[17] deal with poorly nourished children showing a considerable degree of retardation in growth and development, and all failed to find a significant stimulatory effect of orally administered vitamin B_{12} despite the relatively large numbers and careful balancing of control and placebo groups. Moreover, Downing,[18] Mitchell *et al.*,[19] and Rascoff *et al.*,[20] administering vitamin B_{12} to premature infants, were unable to demonstrate any significant effect on growth. The second paper by Wetzel[7] gave additional data to support his original hypothesis but as before did not make use of placebo controls. More recently, Montoye *et al.*[21] found no positive effect of vitamin B_{12} administration to school children, and Howe[1] cites a dissertation by Wittich[22] in which this vitamin stimulated the growth of school children.

The present study is an attempt to determine with reasonable certainty whether or not 20 μg of vitamin B_{12} administered daily by mouth has any tendency to improve the growth of rural Guatemalan children of either preschool or school age. The growth and development of these children were, on the average, markedly retarded, and their intake of protein of animal origin extremely low. The trials were run concurrently with those of Mackay *et al.*[17] in Jamaica and have yielded similar results.

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TABLE I

Average Monthly Height and Weight Gains of Preschool Children Given Orally 20 μg Vitamin B_{12} Daily

Period	Height (cm)		Weight (kg)	
	Control	B_{12}	Control	B_{12}
	N = 26	N = 24	N = 26	N = 24
I	0.70	0.65	0.16	0.17
	N = 15	N = 20	N = 15	N = 20
II	0.48	0.43	0.18	0.17
	Approx. L.S.D.$_{0.05}$ = 0.08 cm		Approx. L.S.D.$_{0.05}$ = 0.05 kg	

MATERIAL AND METHODS

Fifty preschool children in the small rural highland village of San Lorenzo el Cubo (SLC) and 228 school children in four other villages—Magdalena Milpas Altas (MMA), Santa María Cauqué (SMC), San Antonio las Flores (SAF), and Chinautla (CHI)—in the same area were ranked by age and sex and randomly assigned to placebo or experimental groups. Tablets containing 20 μg of vitamin B_{12} or placebo identical in appearance were administered daily by mouth six days a week. In physical appearance and development, social and economic status, as well as dietary habits, the children included in this study were similar to those described for previous field experiments.[15,23] Their diets provided protein of animal origin in the range of only 8 to 14 g daily and their height, weight, and bone maturation were approximately two to four years behind those of well-nourished children of comparable age in the United States and Guatemala. All children were eating ad libitum in their own homes throughout the study.

Height and weight measurements were obtained monthly and a careful record of attendance kept. Personnel administering the tablets had no knowledge as to which children were receiving placebos. It was possible to administer the treatment without substantial interruption to preschool children, but treatment of the school children was discontinued during the school vacation, from October through December. The study of preschool children was begun in October, 1954, and terminated in October, 1955; that of school children was started in March, 1954, and finished in October, 1955, during 12 weeks of which time they were on vacation and did not receive treatment.

Both height and weight gains were adjusted by multiple regression methods for initial differences in age, height, and weight. No effect of frequency of treatment was encountered, so that no correction for this variable was made in the data presented. The approximate least significant differences ($\alpha = 0.05$) were calculated using pooled estimates of error.

RESULTS

The results of the administration of vitamin B_{12} to the preschool children are shown in Table I. There is no suggestion in these data of a positive effect of vitamin B_{12} at this dose on rate of gain in either height or weight.

Similarly, the data for the school children (Table II) make possible twelve sets of com-

TABLE II

Average Monthly Gains of School Children Given Orally 20 μg Vitamin B_{12} Daily

Village	First 6 mo		Second 6 mo		Third 6 mo	
	Control	B_{12}	Control	B_{12}	Control	B_{12}
Height (*cm*)						
MMA	0.36	0.37	0.41	0.36	0.42	0.36°
SMC	0.41	0.37	0.42	0.53°	0.43	0.42
SAF	0.42	0.45	0.44	0.45	0.47	0.44
CHI	0.37	0.34	0.51	0.46	0.27	0.26
Weight (*kg*)						
MMA	0.18	0.20	0.11	0.08	0.22	0.20
SMC	0.14	0.12	0.18	0.26°	0.20	0.16
SAF	0.19	0.22	0.18	0.14	0.20	0.19
CHI	0.18	0.21	0.08	0.08	0.19	0.21

Approx. L.S.D.$_{0.05}$ = 0.06 cm in height; 0.06 kg in weight. ° Indicates significant differences.
Approx. Number: MMA-83, SMC-53, SAF-58, CHI-34.

parisons, one for each of three 6-month periods in four villages. Of the twelve comparisons for the effect of vitamin B_{12} on height, one is significantly positive, one significantly negative, and ten show no effect. Of those for weight, eleven show no significant difference. The single period in which a positive effect on height and weight was observed in one village had the lowest frequency of treatment due to the 3-month school vacation.

DISCUSSION

The data presented provide no basis for assuming that vitamin B_{12} has any effect, positive or negative, on growth as estimated by the rate of gain in either height or weight. Although subjective benefits from vitamin B_{12} administration have often been mentioned in the literature, such alterations as were noted by teachers and field workers in our experiment seemed to occur with equal frequency in the experimental and control groups. The data available did not permit any further attempt to appraise subjective changes.

It was felt that such a study in a population known to be greatly retarded in growth and development and subsisting on a diet containing sufficient calories and total protein but only a small amount of animal protein would give the maximum opportunity for demonstrating a vitamin B_{12} effect. Even if the effect of vitamin B_{12} were only to stimulate appetite, the children should have been able to show a response, since they were on an ad libitum diet which was limited more by quality than quantity, and in most cases a child could have had greater quantities of food if he had desired it. It is noteworthy that our results are identical with those of a parallel field trial by Mackay *et al.*[17] and also those of Someswara Rao *et al.*,[16] whose studies failed to show a positive effect on undernourished Jamaican and Indian children, respectively.

In view of the earlier concept that vitamin B_{12} might improve the growth of children on diets low in animal protein by supplying a missing "animal protein factor" or by improving the utilization of protein of vegetable origin, the studies by Someswara Rao *et al.*[16] in undernourished Indian children, Kaye *et al.*,[24] and Chow *et al.*[3] in infants 3–6 and 3–12 months of age are significant. All these studies failed to demonstrate a significant effect of vitamin B_{12} on nitrogen retention, although the Indian workers tested it as an addition to both restricted and adequate vegetarian diets and the other investigators studied it with intakes of high and low protein content. Closely related to the problem is the failure of Aguirre and Scrimshaw[25] to find any effect of vitamin B_{12} on hematologic values in the same or similar children.

It is possible in theory, as Howe[1] suggests, that these children would have responded to vitamin B_{12} administration if some other factor had not been more limiting. Although the design of the present study does not specifically exclude such a possibility, previous trials in both Guatemala and El Salvador[15] failed to demonstrate a statistically significant difference between vitamin B_{12} and placebo when included in dietary supplements designed to make up existing deficiencies. Although the intake of vitamin A in these trials was below the recommended dietary allowance, subsequent experiences indicate that this vitamin was not a limiting factor.

Many of the reported studies suffer from deficiencies in experimental design and interpretation of the data which make them inconclusive. One is the danger of using children of one village as a control and those of another as an experimental group. The difference in growth rates among villages shown in Table II is such that any conclusion could have been obtained by chance, had this practice been followed in the present study. Equally unreliable is the use of a group as "its own control." The variations from one 6-month period to the next are so great that had the previous or subsequent growth experience of any of these groups been used for comparison with a period of vitamin B_{12} administration, again any conclusion could have been obtained fortuitously. Another procedure has been to pick out those children in an experimental group showing growth spurts during the experimental period and call attention to them as examples of significant and unexpected response. Analysis of our own data has shown that individual spurts

of growth during an experimental period are equaled by individual spurts in the control groups, and our groups are of sufficient size to validate this observation.

We also feel that undue significance has been attached in some studies to the month-to-month fluctuations in the height and weight measurements recorded for individual children. Although the curves for child growth which have been developed from the analysis of the data from large numbers of individuals give the impression of a smooth progression, many individuals do not follow such a pattern in a regular manner. The fine studies of the growth of individual children (Stuart *et al.*[26,27] and Reynolds and Sontag[28]) show that many children grow with types of variation similar to those characterized by some authors as "growth failure" and "growth response."

It is noteworthy that vitamin B_{12} has been without effect in studies conducted in technically underdeveloped areas with children showing some degree of malnutrition and growth retardation. On the basis of these reports and our own experience there would appear to be no indication for the use of vitamin B_{12} in public health or school programs designed to improve the nutritional status of children whose growth and development are retarded.

The present data do not preclude the possibility that occasional apparently well-nourished children whose growth and maturation are chronologically retarded will respond to vitamin B_{12} administration. This question will have to be resolved by additional critical studies among well-nourished groups of children.

SUMMARY

The daily oral administration of 20 μg of vitamin B_{12} in controlled trials involving 50 preschool children in one rural village and 228 school children in four rural schools in Guatemala did not produce any effect on their rates of gain in either height or weight. These data illustrate some of the errors in interpretation which can result from the considerable variation and apparently fortuitous changes commonly observed in the rates of growth and maturation in children. The present findings are in agreement with the results of trials conducted in other areas involving children showing some degree of malnutrition and growth retardation and subsisting on relatively inadequate diets.

On the basis of the foregoing it appears that the growth retardation commonly observed in technically underdeveloped areas will not be affected by the administration of vitamin B_{12}.

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Impairment of Intestinal Absorption of Vitamin A Palmitate in Severe Protein Malnutrition (Kwashiorkor)

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ONE of the consequences of the severe protein malnutrition underlying kwashiorkor is a decrease in the activity of various enzymes as measured in blood serum, tissues, and duodenal contents. Veghélyi,[1] Thompson and Trowell[2] and Gómez *et al.*[3] have reported that the activities of lipase, trypsin, and amylase are reduced in the duodenal secretions of kwashiorkor patients. Of the three enzymes lipase appears to be the first to be affected, followed by trypsin.[1] These biochemical findings are consistent with the histologic damage observed in the pancreas and intestine when the disease is severe.[4,5]

A decrease in pancreatic lipase and in bile salts as well as functional alterations of the small intestine, are known to impair the absorption of vitamin A. In the course of studies in children with kwashiorkor in Central America[6] very low serum levels of vitamin A have been found and ocular lesions suggestive of vitamin A deficiency are observed.

Even though a dietary deficiency of sources of vitamin A or carotene may be partially responsible for these biochemical and clinical findings, the contribution of metabolic and pathologic factors which alter the utilization of the vitamin should also be considered. The present work was designed to study the effect of oral administration of vitamin A palmitate on serum vitamin A levels in children with kwashiorkor before and after therapy.

METHODS AND TECHNIC

A vitamin A "absorption test" was performed according to the recommendations of Mendeloff.[7] A vitamin A palmitate concentrate¶ was diluted with corn oil shortly before use to a final concentration of 10,000 μg/ml; the preparation was kept refrigerated and protected from direct light. The test solution was then administered by stomach tube to the fasting child to provide a net dose of 75,000 μg of vitamin A. Two hours later the subject was given a test meal consisting of either 200 ml of skimmed milk or the same quantity of corn starch gruel; both gave the same type of response. Fingertip blood samples were taken just before the administration of the vitamin and then 1, 2, $2^1/_2$, 3, 4 and 5 hours following the vitamin dose. The two-hour sample was taken immediately prior to the test meal. In this way, seven samples were collected during a period of five hours. A surgical blade was employed to make only one fingertip incision from which the seven 0.5 ml

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¶ General Biochemicals, Inc., Chagrin Falls, Ohio. Vitamin A palmitate in corn oil, 1,000,000 i.u./g.

TABLE I

Total Serum Protein in Serial Fingertip Blood Samples of Children with Kwashiorkor

Case	Days of treatment	Total serum proteins (g/100 ml) at time intervals (hrs) after test dose						
		0	1	2	2½	3	4	5
PC-46	0	—	4.55	4.42	4.45	4.43	4.05	4.05
PC-48	0	—	4.12	4.20	4.14	4.12	4.14	4.02
PC-49	0	3.19	3.17	3.12	3.08	3.00	2.88	2.93
PC-50	0	4.40	4.40	4.40	4.34	4.30	4.00	4.16
PC-52	5	4.32	4.16	4.10	4.20	4.18	4.10	3.70
PC-46	5	5.98	5.60	6.00	5.53	5.42	5.50	5.42
PC-50	5	5.20	5.24	4.92	5.02	4.82	4.85	4.62
A-3	3	5.37	5.37	4.84	5.21	5.07	4.93	4.90
A-4	3	4.85	5.09	5.40	5.35	5.20	5.12	5.37
Completely recovered cases of kwashiorkor								
RPC-1	67	7.26	—	7.23	7.26	7.24	7.28	—
RPC-2	130	6.76	—	7.08	7.12	6.98	7.01	—
RPC-3	315	6.72	—	6.83	6.81	6.83	6.81	—

blood samples could ordinarily be collected by re-opening the wound with pressure, thus causing a minimum of discomfort to the child.

The serum from each sample was stored at −20° C until analyzed for vitamin A and carotene by the microtechnic of Bessey *et al.*[8] In order to evaluate the possible contamination of the blood samples with extracellular exudate (particularly in patients with edema), total proteins were also measured in each individual sample of serum by the method of Lowry and Hunter.[9]

EXPERIMENTAL PROCEDURE AND RESULTS

Children admitted with frank clinical kwashiorkor either to the General Hospital or to the hospital of the "Sociedad Protectora del Niño" in Guatemala City were tested. In the original description of the method a positive response was recorded when the test dose resulted in an increase of the serum vitamin A level to at least four times the fasting concentration or in an absolute peak value greater than 100 μg/100 ml during the test. This gives a large margin of safety in distinguishing a positive response from changes in vitamin A concentration due to variations in plasma volume or to contamination with extracellular exudate. Since in the present work vitamin A palmitate absorption was tested in children employing a technic previously used only in adults, it was decided to re-evaluate the procedure in order to determine the time and magnitude of maximum response in children.

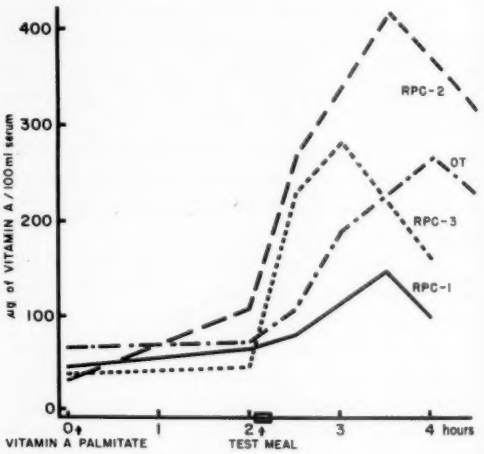

Fig. 1. Response to oral vitamin A palmitate in adequately nourished children. A test dose of 75,000 μg was given to each child and followed by a glass of skimmed milk two hours later. Blood samples for vitamin A analysis were taken at the intervals indicated. The sex and age of these children were as follows: RPC-1 (M), 2 yr, 10 mo; RPC-2 (M), 1 yr, 7 mo; RPC-3 (M), 2 yr, 2 mo and O.T. (F), 3 yr, 2 mo.

For this purpose, the test was run in three hospitalized children who had completely recovered from kwashiorkor (RPC-1,2,3) and on

TABLE II

Serum Carotene in Serial Fingertip Blood Samples of Children with Kwashiorkor

Case	Days of treatment	Serum carotene (μg/100 ml) at time intervals (hrs) after test dose						
		0	1	2	2½	3	4	5
PC-46	0	—	7	3	4	4	4	4
PC-48	0	13	11	10	10	10	10	—
PC-49	0	4	6	4	5	6	5	5
PC-50	0	4	4	3	3	3	3	4
PC-52	5	2	1	1	1	1	1	1
PC-54	5	3	4	2	4	2	3	3
PC-55	5	4	4	3	4	4	4	4
A-3	3	12	11	12	15	13	13	13
No-4	3	5	5	4	5	5	7	7
Completely recovered cases of kwashiorkor								
RPC-1	67	103	—	103	103	102	100	—
RPC-2	130	45	—	46	45	45	44	—
RPC-3	315	12	—	12	12	13	13	—

an outpatient child not suffering from severe malnutrition (OT). Figure 1 shows the rapid rises in serum vitamin A, reaching maximum concentrations within 45 minutes and 1 hour 45 minutes after taking of food, i.e., within three to four hours after the vitamin A administration. The timing of these responses is the same and the magnitude similar to that reported by Mendeloff *et al.*[7] for adults and accordingly their criteria for a positive response have been used in this report. It should be noted that the technic is quite different from that of McCoord *et al.*[10] which requires four to five hours to obtain maximum serum levels after the test dose.

Variations in serial values of total serum proteins for 12 cases randomly selected from the different experiments are illustrated in Table I and indicate changes of such a small magnitude as to have no significant effect on the result of the test. This is also true of the results of carotene determinations in a similarly selected group presented in Table II, which also illustrates the narrow range of variation among the values for each individual child and the extremely low levels of this provitamin in the serum of kwashiorkor patients.

Experiment 1

Eight children with kwashiorkor were admitted for study and given electrolyte therapy for a period of 24 hours according to routine procedures described elsewhere.[11] They were then tested as described above for the ability to absorb vitamin A palmitate. After the trial, a strictly controlled diet was given to the children, consisting of acidified half skimmed milk to provide therapeutic amounts of protein (3 to 5 g/kg body weight); on the fifth day of treatment the test was repeated on five of the patients.

The results obtained in five children who were tested both on hospital admission and the fifth day of therapy are presented in Figure 2. It shows the lack of response to the test on admission as well as the positive response on the fifth day of controlled therapy. Three additional children were tested on admission with negative results; their pre-test vitamin A serum levels were changed from 9, 8 and 14 μg per 100 ml to 13, 10 and 14 μg, respectively.

Experiment 2

In view of the results obtained in experiment 1, the possibility was investigated that the vitamin A given on admission could be determining or influencing the positive response to the test of the same individuals on the fifth day. This could occur either as the result of a therapeutic effect or of adding to the body reserves of vitamin A through slow absorption subsequent to the initial test. Omitting the

test on admission, four children with kwashiorkor were tested after five days and one after four days of the same therapy as in experiment 1. The data presented in Table III show that under these conditions the responses after therapy were still positive, but the peak serum vitamin A levels were not as high as in the children given an initial test dose in experiment 1. The differences between the peaks in these two experiments suggest that significant quantities of the vitamin ester given on admission in experiment 1 were eventually absorbed.

Experiment 3

Another group of children with kwashiorkor was tested as in experiment 2 in order to study the effect of the palmitate after only three days of the therapeutic diet. Comparison of the pre-test serum vitamin A levels with the highest levels obtained after the test dose (Table IV) reveals that only three of the five children showed more than a four-fold increase and that only one gave a response as great as the subjects of experiments 1 and 2 after five days of treatment. Three days appears to be close to the lower limit of time necessary for recovery of the normal ability to absorb the ester under the conditions of the experiment, and not all patients recovered this rapidly even with good therapy.

Experiment 4

Nine additional cases of kwashiorkor in the pediatric ward of the General Hospital were studied after three or five days of hospitalization without the initial test on admission. In contrast to the three previous experiments, these children received the regular ward diet *ad libitum* and were not under research control. Table V shows the lack of satisfactory

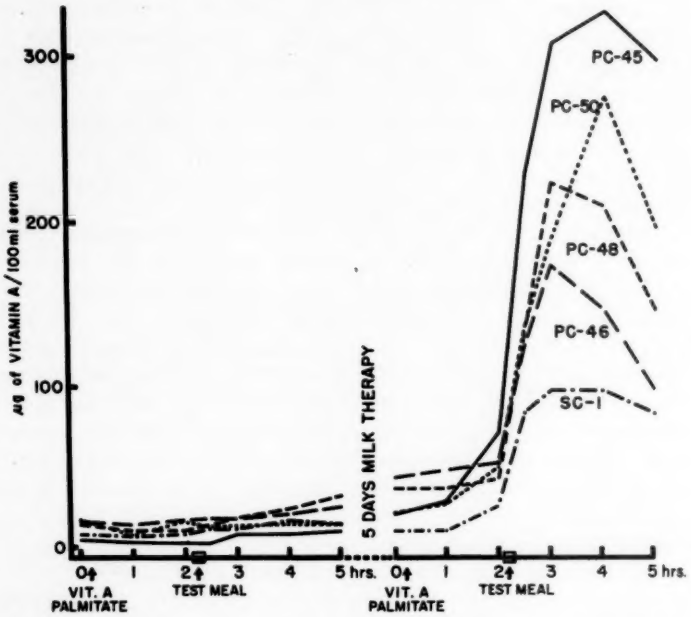

Fig. 2. Response to oral vitamin A palmitate in children with kwashiorkor before and after five days of therapy. After 24 hours of electrolyte therapy children hospitalized for kwashiorkor were given 75,000 μg of vitamin A as palmitate orally followed by a glass of either skimmed milk or corn-starch gruel two hours later. Blood samples for vitamin A analysis were taken at the intervals indicated and the entire test repeated after five days of intensive therapy based on the administration of adequate quantities of half-skimmed milk.

TABLE III

Vitamin A Palmitate Absorption Test in Kwashiorkor after Five Days of Research-Controlled Milk Therapy

Case	Sex and age in years	Serum vitamin A (μg/100 ml)		Peak as multiple of initial value
		Before dose	Peak after dose	
PC-52	M 1.7	2	26	13.0
PC-54	M 2.0	3	46	15.3
PC-55	M 1.4	10	76	7.6
SC-2	F 1.1	24	218	9.1
No-1*	M 4.0	10	87	8.7

* Four days of treatment.

TABLE IV

Vitamin A Palmitate Absorption Test in Kwashiorkor after Three Days of Research-Controlled Milk Therapy

Case	Sex and age in years	Serum vitamin A (μg/100 ml)		Peak as multiple of initial value
		Before dose	Peak after dose	
No-2	M 4.0	16	38	2.4
No-3	M 10.0	2	12	6.0
No-4	M 11.0	3	13	4.3
A-3	F 2.0	13	25	1.9
A-4	F 3.5	34	254	7.5

TABLE V

Vitamin A Palmitate Absorption Test in Kwashiorkor after Three to Five Days of Treatment not under Research Control

Case	Age†	Serum vitamin A (μg/100 ml)		Peak as multiple of initial value
		Before dose	Peak after dose	
Na-1	6.8	11	10	0.9
Na-2*	5.0	14	27	1.9
Na-3*	4.0	9	14	1.6
Na-5*	4.0	20	20	1.0
Na-7	4.0	2	3	1.5
Na-8	4.0	1	3	3.0
Na-9	5.0	20	30	1.5
Na-10	3.2	23	45	2.0
Na-11	5.1	19	28	1.5

* After five days of treatment, others after three days.

† All subjects were female.

response to the test under these therapeutic conditions. Since anorexia is a characteristic of the syndrome, it is reasonable to assume that the *ad libitum* dietary intake of the patients during the three to five-day experimental period was insufficient to produce a therapeutic response.

DISCUSSION

The results suggest that the vitamin A "absorption test," as recommended by Mendeloff,[7] is a sensitive indicator of functional impairment of the intestinal uptake of vitamin A palmitate. The direct cause, however, of the failure of vitamin A palmitate to appear in the blood stream in kwashiorkor, following an oral test dose, cannot be definitely determined from the results of the present investigation, since the disease results in a number of structural and biochemical changes which could be wholly or partly responsible. Histologic studies of the liver have revealed in all cases a high degree of fatty change. Although most of the classic liver function tests have failed to indicate a generalized hepatic dysfunction[12,13] direct examination of the bile obtained from the gallbladder in necropsy studies has shown it to be scanty, thin and mucus-like in consistency and with a golden yellow color instead of the normal dark green.[14]

Furthermore, histologic studies of the intestine itself leave no doubt as to the extensive atrophy with marked diminution in the number and size of the Kerckring's valves, atrophic degeneration of the Lieberkühn's crypts, as well as a reduction in epithelial and Paneth cells.[5] Finally there is a marked decrease in lipase activity, secondary to serious pancreatic disease.[4,5,15]

Whatever the causes may be, the response shown by patients fed therapeutic amounts of milk proteins is remarkably rapid. Studies of digestive enzyme changes during treatment have also clearly demonstrated a return to physiologically satisfactory levels in three to four days of therapy.[1] It is possible that the response to the vitamin A "absorption test" is dependent primarily on the availability of pancreatic lipase. Certainly tests of this type are commonly used as indicators of the capacity to absorb fat. Moreover, Gómez *et al.*[16] have shown a significantly reduced fat absorption in malnourished children admitted to the hospital whether macroscopic steatorrhea was present or not.

The low carotene and vitamin A content of

the Central American diets which result in kwashiorkor[17] may contribute to the lower serum levels of these factors. If, however, the deficiency of protein is so severe that the normal intestinal absorption of vitamin A is markedly decreased, satisfactory vitamin A serum levels will not be maintained regardless of the dietary content of this vitamin. Low levels of vitamin E also have been found in kwashiorkor by Trowell, Moore and Sharman[18] in Uganda and Scrimshaw *et al.*[6] in Central America. Trowell suggests that the reduced levels of serum vitamin E may be another consequence of a general impairment in the intestinal absorption of fat-soluble factors in the syndrome.

SUMMARY

The effect of an oral dose of 75,000 μg of vitamin A as palmitate on vitamin A serum levels has been tested in children suffering from kwashiorkor. It was found that on admission, this amount of the vitamin ester had no detectable effect on serum levels. After dietary treatment based exclusively on therapeutic amounts of acidified half skimmed milk, the test dose resulted in very marked serum vitamin A increases as early as the fifth day, and in some patients even by the third day of treatment. In another group of children an unsupervised *ad libitum* diet failed to produce this change in three to five days.

The possible relation of these observations to histopathologic and biochemical alterations in the pancreas, liver and intestine is discussed. It is suggested that the low levels of serum vitamin A found in kwashiorkor may be a consequence of a generalized failure to absorb fat-soluble factors.

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Electrolyte Disturbance in Acute Alcoholism

With Particular Reference to Magnesium

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A STUDY of serum electrolyte levels in the alcoholic was undertaken in view of the reports from Flink and his associates[1,2] of the frequent occurrence of low serum magnesium levels in the chronic alcoholic with delirium tremens, with the improvement of the tremor, handwriting, and hallucinations in these patients occurring with magnesium therapy. As other electrolyte changes were not documented except for mention of occasional hypopotassemia and hypophosphatemia, and absence of hypocalcemia, it appeared important to study the serum electrolyte pattern.

MATERIAL AND METHODS

Forty-four patients who entered the hospital with acute alcoholism, the majority with hallucinations and severe tremor, were the subjects. On entry 17 patients had hallucinations, 39 had tremor, 2 had convulsions, and 5 were violent, requiring full leather restraints. While an adequate history was not obtained on all patients due to the mental confusion it was ascertained that 21 of the patients were chronic alcoholics, 2 were periodic drinkers, and 5 were acute alcoholics. Only one patient had ascites. The duration of alcoholism was not determined in 16 of the patients.

On entry to the hospital or soon thereafter, blood was drawn for determination of serum magnesium, sodium, potassium, calcium, chloride, phosphate, and serum water levels. Samples were obtained in 30 of the patients prior to any therapy. One or more determinations of serum electrolytes were made in 28 of the patients.

The serum magnesium level was determined by the method of Simonsen.[3§] The other serum electrolytes were determined by methods previously reported from this laboratory.[4] Serum water was determined by the gravimetric method, after drying to constant weight.

Handwriting samples were obtained on entry in all patients who were not violent and who were not restrained (26 patients). Several samples of handwriting were taken during hospitalization in a small group of patients. A clinical estimate of mental state and degree of tremor was also made.

Five of the patients received magnesium therapy. Only serum magnesium levels obtained before magnesium therapy are included in this paper, as the amounts and routes of magnesium therapy were too variable for comment on effect.

The majority of the patients received intensive therapy consisting of hydration, intravenous glucose, vitamins, and Thorazine and were discharged within 24 hours. A few patients required several days of hospitalization.

RESULTS

Table I summarizes the entry serum electrolyte levels in 30 patients, expressed as percentage of the determinations which were low, normal, or elevated. Thirty-six and six-tenths per cent of the serum sodium and 27 per cent of the serum chloride levels were elevated on entry, in contrast to infrequent elevation of the other serum electrolyte levels. Sixty

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§ Flink used both the method of Simonsen and the Titan Yellow method, so his results can be readily compared to ours.

TABLE I

Serum Electrolyte Levels Before Therapy (30 Patients)

	Low	Normal	High
Sodium	6.7	56.6	36.6
Potassium	30	70	—
Magnesium	60	30	10
Calcium	20	80	—
Chlorine	6.7	6.7	26.7
Phosphate[a]	13.6	72.7	13.6

Figures are per cent of total number of determinations.

[a] Twenty-two patients.

per cent of the serum magnesium determinations, 30 per cent of the serum potassium, 20 per cent of the serum calcium, and 13.6 per cent of the serum phosphate levels were below the normal range, while only 6.7 per cent of the serum sodium and chloride levels were below normal.*

All the entry serum water levels were essentially normal except for 4 patients who had a slight decrease in level (88.8–89.5). Severe dehydration was noted clinically in only 4 patients. All of these patients had either normal or elevated serum magnesium levels.

The electrolyte values on days 1–4 in the patients followed serially are summarized in Table II. Following hydration and sedation during the first 24 hours, 90 per cent of the serum chloride levels, 80 per cent of the serum calcium, and 70 per cent of the sodium levels were in the normal range, compared to only 20 per cent of the serum magnesium and 50 per cent of the serum potassium levels. By day 3, in the 8 patients studied, three-fourths or more of the sodium, potassium, calcium, chloride, and phosphate levels were normal, compared to only 50 per cent of the serum magnesium levels.

Handwriting samples were taken on entry in 26 patients, in 11 patients during the first 24 hours in the hospital, in 6 patients on the second hospital day, and in 6 patients after the second day. The handwriting samples were graded into 4 categories (normal, moderate tremor, marked tremor, complete illegibility) by one of the authors who did not know the serum magnesium levels. The classification of the handwriting was then correlated with the serum magnesium level (Table III and Table IV).

On entry, except for the patients whose handwriting was completely illegible and who all had low serum magnesium levels, there appeared to be little general correlation between serum magnesium levels and handwriting. Approximately 50 per cent of the serum magnesium levels were low or normal with either normal or tremulous handwriting. When all the handwriting samples from entry to hospital day 5 were correlated with the serum magnesium levels (see Table IV) the same general lack of correlation was also found, except for those with illegible handwriting.

Illustrations of handwriting correlated with the serum magnesium level are shown in Figures 1 and 2. Figure 1 shows marked improvement in handwriting in 48 hours, with no improvement in the serum magnesium level

* Values reported previously in abstract form[5] gave slightly different percentages, as a few patients were included in the entry group who had received a small amount of intravenous fluid before blood was drawn for the serum electrolyte determinations.

TABLE II

Serum Electrolytes After Entry

	Day 1 (10 patients)			Day 2 (7 patients)			Day 3 (8 patients)			Day 4 (3 patients)		
	Low	Normal	High	Low	Normal	High	Low	Normal	High	Low	Normal	High
Sodium	20	70	10	14	57	29	13	74	13	—	100	—
Potassium	50	50	—	29	71	—	25	75	—	33	67	—
Magnesium	70	20	10	43	57	—	50	50	—	33	67	—
Calcium	20	80	—	43	57	—	13	87	—	33	67	—
Chloride	—	90[a]	10	—	100[c]	—	13	74	13	—	67	33
Phosphate	—	88[b]	12	—	100	—	17[d]	83	—	—	100	—

Figures are per cent of total number of determinations.

[a] 9 patients; [b] 8 patients; [c] 6 patients; [d] 6 patients.

TABLE III

Entry Handwriting and Serum Magnesium Levels (26 Patients)

Character of handwriting	No. patients	% Normal or slightly elevated (1.53–1.84+ meq/l)	% Slightly low (1.26–1.52 meq/l)	% Low (1–1.25 meq/l)	% Very low (under 1 meq/l)
Normal	6	50	17	33	—
Moderate tremor	10	50	20	20	10
Marked tremor	7	43	28.5	28.5	—
Illegible	3	—	—	67	33

(1.01 meq/l on entry and 0.75 meq/l at 48 hours). Figure 2 shows a fairly legible but tremulous handwriting on entry in another patient. At this time the serum magnesium

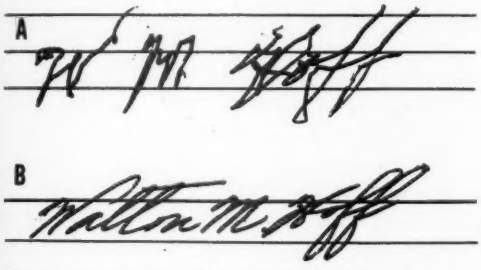

Fig. 1. Improvement in handwriting with no improvement in serum magnesium level. *A*, handwriting at entry; serum magnesium 1.01 meq/l. *B*, handwriting on day 3; serum magnesium 0.75 meq/l. Patient: Walton M. Hoff.

level was 1.42 meq/l. Ten hours later, following hydration, the serum magnesium level was 1.24 meq/l, and the handwriting at this time had become completely illegible.

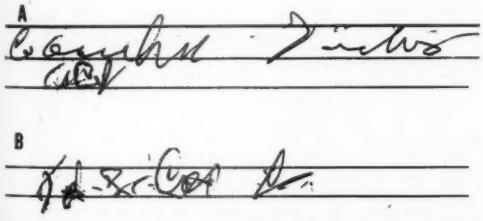

Fig. 2. Change in handwriting (decrease in legibility) with only slight change in serum magnesium level. *A*, handwriting at entry; serum magnesium 1.42 meq/l. *B*, handwriting 10 hours later; serum magnesium 1.24 meq/l. Patient: Concha Fisher.

TABLE IV

Correlation of All Handwriting Samples Obtained and Serum Magnesium Levels (49 Patients[a])

Character of handwriting	No. patients	% Normal or slightly elevated (1.53–1.84+ meq/l)	% Slightly low (1.26–1.52 meq/l)	% Low (1–1.25 meq/l)	% Very low (under 1 meq/l)
Normal	14	43	29	14	14
Moderate tremor	23	43	26	22	9
Marked tremor	8	50	25	25	—
Illegible	4	25	—	50	25

[a] Same patient may be listed more than once if serial magnesium levels were determined.

TABLE V

Correlation of Hallucinations and Tremor with Serum Magnesium Level[a]

Clinical state	No. patients	% Normal or slightly elevated (1.53–1.84+ meq/l)	% Low (1.0–1.52 meq/l)	% Very low (under 1 meq/l)
Hallucinations	16	63	31	6
No hallucinations	48	48	44	8
Tremor	57	46	47	7
No tremor	12	67	25	8

[a] Same patient may be listed more than once if serial magnesium levels were determined.

Little correlation is seen between the serum magnesium level and the presence or absence of hallucinations (Table V). A few more patients with tremor, however, had low serum magnesium levels.

DISCUSSION

Our results confirm the important finding of Flink[1,2] of the occurrence of low serum magnesium levels in the chronic alcoholic with delirium tremens. We were unable to correlate clinical symptomatology with the serum magnesium level in most instances. This was true of some patients in Flink's series also. The improvement in handwriting and tremor which he noted after magnesium therapy occurred in many of our patients who received only

hydration, intravenous glucose, vitamins, and sedation, and no magnesium. The situation may be analogous to that occurring with potassium, where serum levels do not always reflect cellular levels and where the symptoms and signs of potassium deficiency cannot always be correlated with the serum level.

The relationship of serum magnesium changes to other electrolyte changes in the alcoholic, a problem which had not previously been adequately studied, has been determined. Our studies demonstrate the important finding that low serum magnesium levels occur more frequently and last longer than other electrolyte changes.

The occurrence of changes in serum electrolyte levels other than magnesium in the acute alcoholic, however, we feel is significant. Previous studies[6,7] have documented the occurrence of potassium deficiency in the chronic alcoholic with cirrhosis. This change is confirmed by our studies. The occurrence of hypernatremia and hyperchloremia in the acute alcoholic has not to our knowledge been mentioned previously. Further, hypocalcemia as a relatively common facet of the electrolyte problem in the acute alcoholic has not been stressed.

The mechanisms responsible for the changes in the serum electrolytes found in the alcoholic require further study. Several suggestions for these changes might be made, however. The drop in the level of the primarily intracellular electrolytes (potassium, magnesium, phosphate) might occur due to poor food intake, plus poor gastrointestinal absorption, and in some instances loss by vomiting and diarrhea. The effect of starvation on serum electrolyte levels is complicated, and no absolute pattern has been found.[8,9] An important factor might be accelerated urinary loss of electrolytes. While a completely normal man may conserve magnesium rigorously on a virtually magnesium-free intake,[10,11] it takes several days for renal conservation to become fully operative. The same situation occurs with potassium, where renal conservation in the normal man may also become adequate after several days.[12] It is well known, however, that starvation and dehydration lead to accelerated loss of potassium over nitrogen in the urine.[13] The same situation may be true as far as magnesium is concerned. The alcoholic usually has serious nutritional problems.

Poor gastrointestinal absorption secondary to vitamin deficiency and such pathologic changes as alcoholic gastritis might well explain alterations of serum calcium and phosphate. Semistarvation also has been shown to cause a fall in serum calcium levels.[9] Alterations of pancreatic function secondary to pancreatitis might also be a factor but was not present in our series, except in one patient who had acute pancreatitis.

The occurrence of hypernatremia and hyperchloremia in about one-third of the patients is of great interest, and suggests disruption of the normal mechanisms which guard the osmolarity of the body fluids. It has been shown that water diuresis, with loss of more water than electrolyte, with decrease in urine osmolarity, occurs in experimentally induced mild acute alcoholism via a probable effect on antidiuretic hormone.[14] This factor could explain the occurrence of the hypernatremia and hyperchloremia.

As magnesium is vitally concerned with enzyme systems in the liver and skeletal and heart muscle which are necessary for carbohydrate and protein metabolism,[15] the depletion of body magnesium which is probably present when the serum levels are low acquires great importance. Further, magnesium deficiency, particularly in the young animal of many species, has been shown to cause necrosis and hemorrhage in the brain and heart, alterations in liver and kidney (nephrocalcinosis), and poor growth.[16–23]

Potassium deficits also are associated with histologic changes (necrosis) in skeletal and cardiac muscle.[24] Chronic severe potassium deficiency may also lead to distal tubular epithelial change, with resultant polyuria and urinary potassium loss.[25]

These facts suggest the importance of correction of the electrolyte alterations which occur in the alcoholic, by adequate magnesium, calcium, and potassium therapy, and hydration for states of hypernatremia and hyperchloremia.

SUMMARY

Serum electrolyte determinations were made in 30 patients with acute, severe alcoholism before any therapy was given. Sixty per cent of the serum magnesium levels, 30 per cent of the serum potassium levels, and 20 per cent of the serum calcium levels were below the normal range. Approximately one-third of the patients showed hypernatremia and hyperchloremia.

There was little correlation in most patients between serum magnesium levels and such clinical findings as hallucinations, tremor, and tremulous handwriting. All but one of the patients with completely illegible handwriting had low serum magnesium levels.

Possible mechanisms suggested for the alterations in the serum electrolytes included poor food and electrolyte intake, poor gastrointestinal absorption, and accelerated urinary loss of electrolytes due to effects of starvation and dehydration. Water diuresis, a demonstrated effect of alcohol, might explain the occurrence of hypernatremia and hyperchloremia in some patients.

The need for adequate fluid and electrolyte therapy in the treatment of the acute alcoholic was stressed in view of the deleterious effects of altered body electrolytes.

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Water, taken in moderation, cannot hurt anybody.—MARK TWAIN

A Method for the Determination of Carotene and Vitamin A in Human Blood Serum

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IN THE course of a study of serum vitamin A and carotene amongst the population of Ruanda-Urundi, we found it necessary to examine the antimony trichloride technic.

There is a very great deal of literature on the subject of the Carr-Price test for the determination of serum vitamin A and carotene, and extensive literature surveys and discussions of this method can be found in several handbooks and papers.[1–6] Very few authors give a complete description of the method used, whereas in this technic, details may be very important and may greatly influence the results. For example, the purity or the lack of purity of the solvents employed (of the chloroform in particular) may cause many difficulties and errors. Widely varying figures have been reported in the literature as "normal" values for vitamin A concentrations, and we believe this may be, at least partly, due to differences in the technics used for the determinations by the various workers. We have therefore decided to give a detailed account of the method we used.

To determine the reproducibility of the vitamin A and carotene determinations, a series of sera were analyzed twice. It was found that the difference in the results between duplicates did not exceed 5 per cent for both carotene and vitamin A. The recovery of known amounts of vitamin A to serum is better than 95 per cent.

APPARATUS

For the routine determinations, a Model 14 Coleman Universal Spectrophotometer was used, with Coleman type 14-302 round cuvettes (19 x 105 mm), pairs of which had been matched in our laboratory to within less than 0.1 per cent transmission. A 14-214 (PC4) filter was used in this spectrophotometer for all the work described here. All readings on the Coleman 14 were taken from the transmission figures on the galvanometer scale.

For checking the purity of the standards and the solvents a Unicam SP 500 Photo-electric Quartz Spectrophotometer was used, with square quartz cuvettes having a 10 mm light path (accurate to within ±0.02 mm), pairs of which had been matched in our laboratory to within less than 0.1 per cent transmission. Red low-actinic glassware was used throughout the procedure (spectral transmission 0–12 per cent in the range from 3,000 to 6,000 angstrom). The temperature in the laboratory where the work was done was kept at 20° C.

SOLVENTS AND REAGENTS

Commercially available "laboratory reagent" type solvents are usually not good enough for spectrophotometry and additional precautions have to be taken before using these solvents. The solvents used for this work were purified according to the following procedures, some of which are in use in the Centraal Instituut voor Voedings Onderzoek, Utrecht, Holland, and were kindly communicated to us by Dr. C. Engel.

(1) *Ethanol*

Analytical reagent grade absolute ethyl alcohol was refluxed for 30 minutes in the presence of 5–10 g of aluminum powder and 5–10 g of KOH (analytical reagent) per liter of alcohol. After refluxing for 30 min, the mix-

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ture was distilled through a 68-cm long column and the light and heavy fractions were discarded; each of these fractions represented 10 per cent of the original total volume of the alcohol.

The ethanol gave a transmission reading of 100 per cent at the wavelengths used in our work when checked against bi-distilled water.

(2) *Petroleum Ether*

Analytical reagent grade petroleum ether, boiling range 40–60° C, was refluxed for 2 hours in the presence of 60 ml concentrated H_2SO_4 per liter of petroleum ether. After cooling, the sulfuric acid layer was removed (separating funnel). This operation was done three times altogether with fresh sulfuric acid.

The petroleum ether was washed in a separating funnel with distilled water until the wash waters no longer showed an acid reaction to Congo-red test paper.

The petroleum ether was dried overnight over anhydrous magnesium sulfate; the magnesium sulfate was filtered off and the solvent was distilled through a 68-cm long column in the presence of a few pellets of sodium hydroxide (analytical reagent grade).

Light and heavy fractions each representing 5 per cent of the total starting volume were discarded.

The petroleum ether gave 100 per cent transmission reading when checked against bi-distilled water at the required wavelengths.

(3) *Chloroform*

Analytical grade chloroform was washed three times with a 10 per cent aqueous solution of sodium thiosulfate. It was then dried overnight over anhydrous calcium chloride, and filtered. The filtered chloroform was shaken with finely powdered anhydrous sodium thiosulfate of "analytical reagent" grade, and filtered again. The chloroform was fractionated, using a 68-cm long column. "Light" and "heavy" fractions each representing about 20 per cent of the total starting volume were discarded. Particular care was taken to use perfectly dry apparatus and to avoid strong light during all operations. Half a per cent (by volume) of absolute ethyl alcohol (purified for spectrophotometric work) was added to the chloroform after the fractionation. We found it better not to use recovered chloroform.

(4) *Antimony Trichloride Reagent*

British Drug Houses antimony trichloride solution in chloroform was used. This solution comes sealed in brown glass 500 ml ampules and contains 86.1 per cent chloroform and 13.6 per cent $SbCl_3$ (corresponding to 8.85 per cent w/w Sb_2O_3). The reagent was measured with the British Drug Houses automatic antimony trichloride pipette specially made for this purpose. We checked the accuracy of the calibration of these pipettes.

STANDARDS USED FOR ESTABLISHING THE CALIBRATION CURVES

(1) *Vitamin A*

For vitamin A, we used the standard solution prepared for the first international collaborative experiment organized in 1955 by the Vitamin Commission of the Food Division of the Applied Chemistry Section of the International Union of Pure and Applied Chemistry. We are very grateful to this organization for donating the standard. It is pure all-trans synthetic vitamin A acetate made by l'Alimentation Equilibrée (France), Distillation Products (U.S.A.), and Hoffmann-La Roche (Switzerland) mixed and dissolved in oil. The potency of that solution as determined by the international collaborative experiment is 98,800 I.U./g of oil.

We repeated this international collaborative test, following exactly the procedure which had been used for that experiment and which was given to us by the chairman of the Vitamin Commission, using our Unicam SP500 Photoelectric Quartz Spectrophotometer.

The results we obtained were in excellent agreement with those found in the collaborative test and quite near the maximum of the Gauss distribution curve of the results from the 36 laboratories who had taken part in that test. This confirmed the reliability of our apparatus,

technic, reagents and vitamin A standard.

(2) *Beta-Carotene*

Pure all-trans β-carotene kindly given to us by Hoffmann-La Roche (Switzerland) was used. This product, after drying in a high vacuum drying pistol, gave an E-value (1 g/liter, 1 cm) of 251.8 at 451 mμ in *n*-hexane.

It had absorption maxima in the same solvent at 451 and 479 mμ and an absorption minimum at 468 mμ.[2]

We used British Drug Houses "Hexane fraction from petroleum special for spectroscopy" which gave 100 per cent transmission when checked against bi-distilled water at the required wavelengths.

TECHNIC USED FOR THE DETERMINATION OF VITAMIN A AND CAROTENE IN BLOOD SERUM

Three ml of serum were pipetted into a 15 ml centrifuge tube. Three ml of freshly prepared KOH N/1 in 90 per cent ethanol were added very slowly with shaking.

The mixture was saponified under reflux for 20 minutes at 50–60° C in a water bath. It was cooled and 6 ml of petroleum ether 40–60° C were added. The tube was then shaken very vigorously by hand for 10 minutes. It was centrifuged for 1 minute at 500 r.p.m., 5 ml of the petroleum ether layer were pipetted off into a Coleman cuvette, containing 2 ml of petroleum ether. These 2 ml of petroleum ether were added to bring the level in the cuvettes up to the required height for the light beam.

The transmission of this solution was read on the Coleman 14 spectrophotometer at 452 mμ. The solvent was then evaporated from the Coleman cuvette by warming it in a water bath at 50° to 60° C while gently blowing nitrogen into the tube. The last traces of solvent were removed by blowing nitrogen at 20° C. The residue was immediately taken up in 1 ml of chloroform.

The cuvette was then placed in position in the Coleman-14 spectrophotometer. The zero of the instrument was adjusted by inserting the paired cuvette containing 1 ml of chloroform in the light beam and adding 6 ml of the antimony trichloride reagent and one drop of acetic anhydride to it while in position in the instrument. (This zero-setting was repeated before every determination with fresh chloroform and antimony trichloride.) Six ml of the antimony trichloride reagent and one drop of acetic anhydride were added very rapidly to the test cuvette after it had been placed in the light beam. The transmission was read at 620 mμ as soon as the galvanometer spot stopped for a few seconds on the scale.

CALIBRATION CURVE FOR BETA-CAROTENE

Ten dilutions of the pure all-trans beta carotene were made in petroleum ether (boiling range 40–60° C). Direct transmission readings were taken at 452 mμ on the Model 14 Coleman Universal Spectrophotometer. They are plotted against the concentration as ⊙ on graph No. 1. To check whether any β-carotene was lost in saponifying, 13 experiments were done in the following way: 1 ml of each of the petroleum ether solutions of varying concentrations was pipetted into a centrifuge tube, 3 ml of bi-distilled water and 3 ml of KOH N/1 in 90 per cent ethanol were added and the procedure used for serum was applied, adding 5 ml of petroleum ether instead of 6 ml.

The tranmission readings at 452 mμ were plotted on graph 1 as X.

We concluded from this, that saponification did not influence the carotene-content.

The best-fitting curve was calculated from the experimental points using the least squares method.

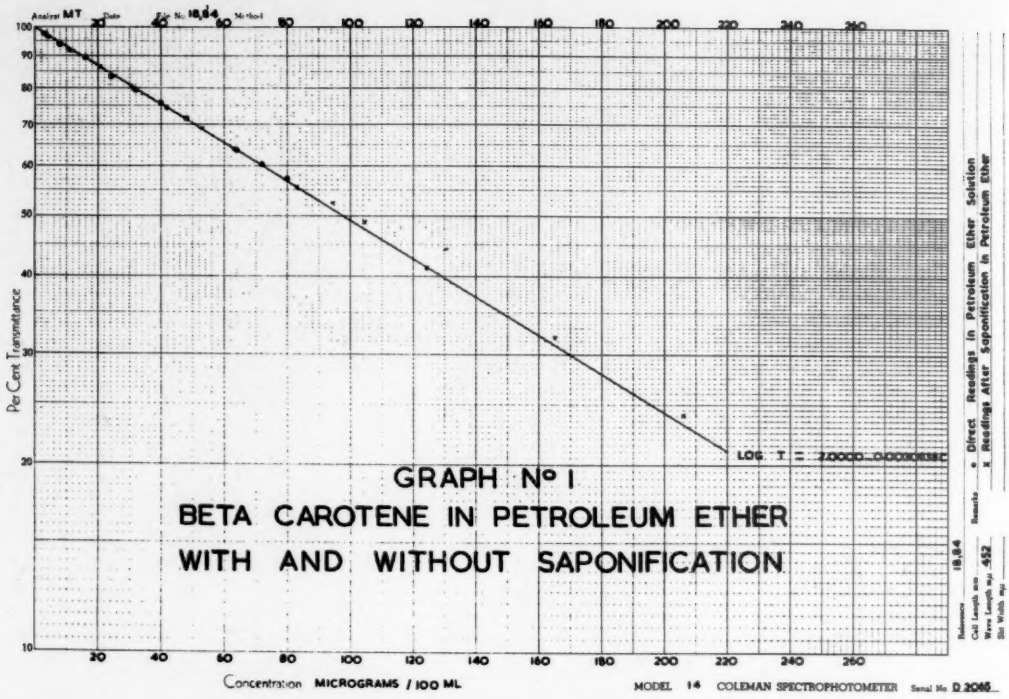
It was found to be $\log T = 2.0000 - 0.0030938\,C$ and is shown on graph No. 1.

CALIBRATION CURVE FOR VITAMIN A

The vitamin A calibration curve is the lower curve shown on graph No. 2.

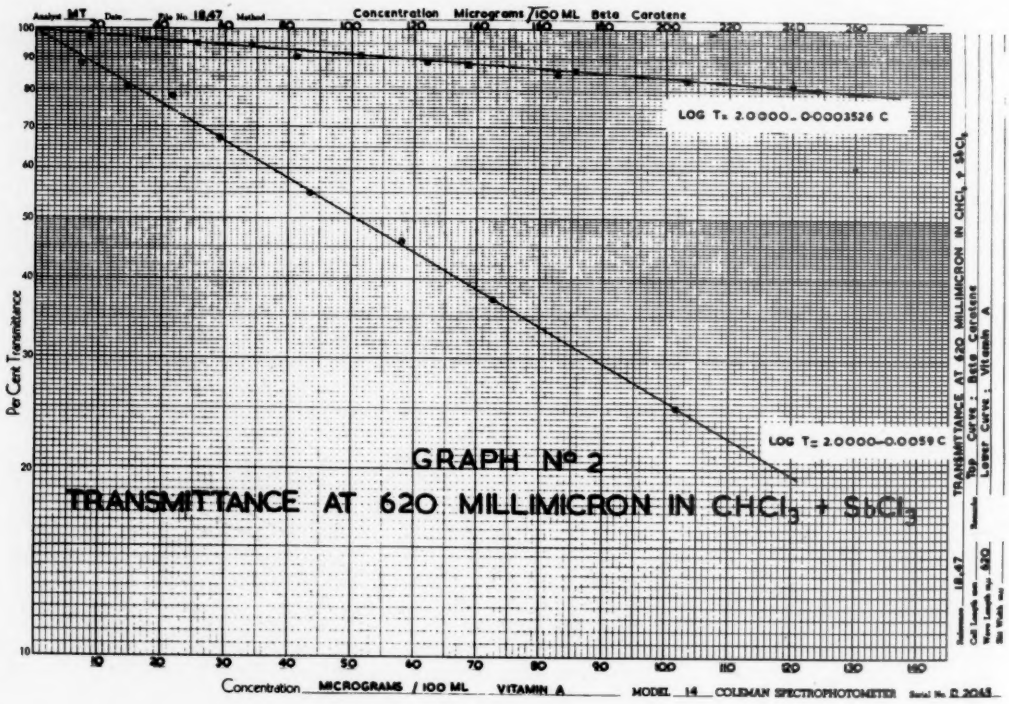
A series of dilutions of the vitamin A standard in absolute ethanol were made. One ml of each of those solutions of known vitamin A concentration was pipetted into a 15 ml centrifuge tube. Two ml of bi-distilled water were added. This gave an aqueous layer of approximately 3 ml.

This was done in order to work under the same circumstances as for the vitamin A determination in the serum, where 3 ml of serum were



GRAPH Nº 1

BETA CAROTENE IN PETROLEUM ETHER WITH AND WITHOUT SAPONIFICATION


Concentration Micrograms / 100 ML Beta Carotene
Per Cent Transmittance
LOG T= 2.0000-0.0003526 C
LOG T= 2.0000-0.0059 C
Concentration MICROGRAMS / 100 ML VITAMIN A
MODEL 14 COLEMAN SPECTROPHOTOMETER

GRAPH Nº 2

TRANSMITTANCE AT 620 MILLIMICRON IN $CHCl_3 + SbCl_3$

used. The same technic as used for serum was then applied.

The transmission at 620 mμ was read and plotted on the graph. The curve was drawn using the equation log $T = 2.0000 - 0.0059$ C. This equation was obtained from the experimental data by means of the least squares method.

METHOD OF CALCULATING CAROTENE AND VITAMIN A CONCENTRATIONS IN THE SERUM

(1) *Carotene*

A table was drawn up enabling us to read directly the carotene concentration in μg per 100 ml of serum from the transmission reading obtained on the spectrophotometer. For this, the concentrations of carotene in the petroleum ether solution obtained from the formula log $T = 2.0000 - 0.0030938$ C had to be multiplied by 2.8; indeed, as is clear from the description of the method used for the determination of vitamin A and carotene in the serum, the extract from $^5/_6$ of 3 ml of serum was dissolved in 7 ml of petroleum ether for reading the transmission on the spectrophotometer.

(2) *Vitamin A*

(A) Correction of the vitamin A transmission reading at 620 mμ for carotene interference at that wavelength. Antimony trichloride in chloroform solution reacts with carotene and the absorption of the reaction product at 620 mμ interferes with the vitamin A determination which is done at the same wavelength.

To determine the extent of this interference, a series of solutions of the β-carotene standard in petroleum ether were made, aliquot portions of it were evaporated from the Colemen cuvettes as described above, taken up in chloroform and antimony trichloride reagent, and the transmissions were read at 620 mμ. The experimental points thus found are shown as ⊙ on graph No. 2 (top curve).

The best-fitting curve was calculated from the experimental points using the least squares method. It was found to be log $T = 2.0000 - 0.0003526$ C and is the top curve on graph No. 2. A second series of solutions of the β-carotene standard in petroleum ether was made, aliquot portions of it were evaporated from centrifuge tubes as described above, and exactly the same procedure was than applied to the residues remaining in the centrifuge tube (after adding 3 ml of bi-distilled water to each tube). as is described for the serum (i.e., saponification, extraction, transmission reading at 452 mμ, evaporation, transmission reading at 620 mμ, in antimony trichloride reagent). It was found that here again, saponification, following the procedure used for the serum analysis, did not influence the transmission readings at 620 mμ of β-carotene in antimony trichloride reagent.

To correct the transmission reading taken on the serum extract at 620 mμ, for the carotene interference, the following method was applied:

The carotene concentration in the serum was calculated from the transmission reading at 452 mμ by means of graph No. 1.

The density at 620 mμ corresponding to this carotene concentration was obtained from the top curve on graph No. 2. This density was subtracted from the density of the serum extract as read on the spectrophotometer at 620 mμ.

(B) Calculation of the vitamin A concentration from the corrected transmission at 620 mμ.

A table was drawn up enabling us to read directly the vitamin A concentration in μg per 100 ml of serum from the density value at 620 mμ, corrected for carotene interference as indicated above. For this, the concentrations of vitamin A in the antimony trichloride reagent, obtained from the equation log $T = 2.0000 - 0.0059$ C corresponding to the lower curve shown in graph No. 2, had to be multiplied by 2.8 because of the difference between the concentrations in the serum and the concentration of the solution in the cell in the spectrophotometer.

SUMMARY

A method for determining total carotene and vitamin A in human serum has been described in detail. The usual procedure of protein precipitation with ethanol, saponification and petroleum ether extraction was followed. Total carotene was measured by a transmission reading at 452 mμ. Vitamin A was

determined according to the Carr-Price method with transmission reading at 620 mμ and correction for carotene interference.

Solvents, standards, reagents, and apparatus used have been described because they may greatly influence the results. The calibration graphs and details of the method for calculating the results have been given.

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Reduction of Ferric Iron to the Ferrous Form During Digestion in Vitro With Saliva

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WORKERS in the field of iron metabolism agree that iron is absorbed more readily by the human being when it is in the ferrous rather than the ferric form, and some even go so far as to believe that iron can be absorbed only in the former state. Most of the iron in food is in the ferric form; thus some reduction probably takes place above or in the upper part of the small intestine from which the greatest quantities of iron are absorbed.

Kirch *et al.*[1] studied the reduction of iron in artificial gastric digestion; later Bergeim and Kirch[2] studied the reduction of iron in samples aspirated from the stomach after the ingestion of ferric chloride and selected foods. Considerable reduction was observed to have occurred. Possibly the process of reduction begins even earlier, perhaps in the mouth or in the upper part of the fundus where salivary digestion may continue under some conditions. The power of saliva to reduce some compounds has long been recognized, but no one, as far as we have been able to discover, has investigated the power of saliva to reduce ferric iron. Therefore, the present study was undertaken to investigate the action of saliva on a ferric salt and also on a ferric salt when food (bread) is present.

MATERIAL AND METHODS

A method had to be found by which both ferric and ferrous forms of iron could be determined in the same digestion mixture. Such a method has been devised by Kirch *et al.*[1] and was adapted for use in the present study. The reaction was carried out in 60-ml pear-shaped separatory funnels. Ten milliliters of 25 per cent hydrochloric acid were placed in each funnel. In rapid succession each of the following was added: 2 ml of saliva which had been incubated with ferric chloride; 10 ml of tertiary butyl alcohol; 10 ml of very cold water; 1 ml of 4 per cent potassium persulfate to those funnels in which all the iron was to be oxidized for the determination of total iron, and 1 ml of water to the other funnels; 5 ml of 20 per cent potassium thiocyanate; and finally 7.5 ml of isobutyl alcohol.

The funnels were shaken for 30 seconds, the layers allowed to separate, the water layer drawn off, and the alcohol layer poured through dry acid-washed cotton. The transmission of color was read in an Evelyn Photoelectric Colorimeter at 490 mμ with a mixture of the two alcohols for reference. Ferrous iron was calculated as the difference between total iron and ferric iron and a correction made for the ferrous iron content of the ferric chloride itself. A standard curve was made from a solution of iron wire in 1N HCl.

A stock solution of ferric chloride was made up in 1N HCl. On each test day 1 ml of the stock solution was diluted to 50 ml with glass-distilled water and added to either 12 or 14 ml of saliva. By this means the acidity of the ferric chloride was low enough that the pH of the saliva to which it was added was lowered only a little. When to 12 ml of saliva the addition of 1 ml of water was replaced by an equivalent amount of ferric chloride, the pH was lowered from 0.25 to 0.35 pH units. Care was taken to minimize the lowering of the pH because Nikiforuk[3] found that saliva had the greatest reducing effect on indicator dyes at pH

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7.5 to 8.0, slightly less at pH 7, and a rapid decline between pH 7.0 and 6.5, the area in which, according to Wessinger,[4] the pH of the saliva of most persons falls. Whether iron would be reduced in a manner similar to dyes was not known.

Four women served as subjects during May and early June. They collected saliva between 9:00 and 10:00 A.M. and again between 12:30 and 1:30 P.M. Lipstick was removed and the teeth were brushed without dentifrice at the conclusion of a meal and no collections made for at least 30 minutes. Paraffin was chewed to induce a flow of saliva. According to Nikiforuk,[3] saliva with the most "sediment (epithelial cells, bacteria, leukocytes and unidentified debris)" has the strongest reducing action on oxidation-reduction indicator dyes. Therefore, the saliva was swirled during the withdrawal of samples for analysis in order to include a representative portion of the sediment.

One milliliter of ferric chloride was placed in a test tube and 12 ml of saliva added to it. The tube was set in a water bath at 36–38°C in a darkened room for 30 minutes. The tube was swirled at the beginning and once during the incubation period. Immediately after removal from the water bath 2-ml portions were delivered into 60-ml separatory funnels and the iron content determined as rapidly as possible to avoid oxidation of the iron that had been reduced. The total iron content of the ferric chloride was 10.6 μg.

RESULTS AND DISCUSSION

The largest percentage of iron reduced by saliva in any single one of the 24 tests was 7.9, but in most tests the percentage was less than 5. The amount reduced was characteristic for the individual: The reducing power of the saliva of subject C was almost negligible, while subject B reduced an average of 7.7 per cent in the morning (Table I). In 10 of the 12 tests made with saliva collected in the morning, more iron was reduced than in samples collected in the afternoon.

Because some of the action of saliva takes place in the fundus of the stomach where air is excluded, and because the absence of oxygen might prevent reoxidation of iron reduced by the digestion medium, a few tests were made under nitrogen. The saliva of subject A was used for four such tests. In two of them the saliva was incubated for 30 minutes, and in two others for 3 hours. Neither the exclu ion of air nor the additional time increased the reduction of iron when no food was present.

The practical question is whether iron is reduced when food and saliva both are present. No doubt the reducing power of foods differs; only bread was employed in the present study. To 1 ml of ferric chloride in a 50-ml centrifuge tube, 14 ml of saliva, and 1 g of dried, ground, unenriched bread were added. Air was replaced with nitrogen in all tests except two. The tubes were incubated for 3 hours except in two tests, when incubation was terminated after 1 hour. The tubes were swirled every 10 minutes. Tubes containing 1 ml of ferric chloride and 14 ml of water were incubated at the same time for the determination of ferrous iron in the ferric chloride solution and the total iron. At the end of the incubation period the tubes containing bread were centrifuged and 2-ml portions of the supernatant liquid drawn off for the determination of iron.

When the saliva of subject A collected in the morning was combined with bread and two tests made in the presence of air, the percentages of reduction of ferric to ferrous iron were 6.7 and 7.7 (Table II); when the air was replaced with nitrogen the percentages rose to 23.5 and 33.7. Since nitrogen increased the reduction so much it was used in the rest of the tests.

The percentages of iron reduced by the saliva of all three subjects were much higher when the saliva was mixed with bread than when saliva

TABLE I
Reduction of Iron in Ferric Chloride[a] by Saliva

No. tests	Subject	Uncombined iron reduced (%)		Combined iron (μg)	
		A.M.	P.M.	A.M.	P.M.
4	A	4.7	3.2	0.3	0.2
2	B	7.7	2.0	0.2	0.1
4	C	1.0	1.2	0.6	0.6
2	D	3.9	2.7	0.5	0.2

[a] The total iron content of the ferric chloride was 10.6 μg.

TABLE II
Reduction of Iron in Ferric Chloride by Bread and Saliva

Subject	Conditions	Uncombined iron reduced (%)		Total iron (μg)		Combined iron (μg)	
		A.M.	P.M.	A.M.	P.M.	A.M.	P.M.
A	3 hr, no N	6.7	—	9.2	—	4.4	—
	3 hr, N	23.5	—	9.2	—	3.8	—
	3 hr, no N	7.7	—	9.6	—	3.4	—
	3 hr, N	33.7	—	9.6	—	2.6	—
	1 hr, N	15.3	7.8	9.1	9.3	4.4	5.4
	3 hr, N	46.9	18.9	9.0	9.0	2.9	4.6
B	3 hr, N	42.8	28.9	9.0	9.0	1.2	3.5
C	3 hr, N	22.3	16.7	9.3	9.3	5.2	5.8

N = nitrogen.

specimens alone were used. The reductions for saliva collected in the morning and incubated for 3 hours under nitrogen ranged from 22.3 to 46.9 per cent and in the afternoon from 16.7 to 28.9 per cent (see Table II). The variability was wide among subjects and for saliva collected from the same subject on different days. Similar wide variation was found by Bergeim and Kirch[2] in gastric digestion. Wide variability might be anticipated because saliva is far from a homogenous mixture. In the present study the addition of bread caused the removal of a high proportion of iron from the solution. Kirch *et al.*[1] found a similar removal of iron by food in gastric digestion mixtures. Presumably the iron combined with the food. Whenever the amount of combined iron was high the percentage of reduction was low. More iron was combined in mixtures containing saliva collected in the afternoon than in those containing saliva collected in the morning.

Apparently the reduction of iron begins with the ingestion of food. It is interesting to speculate whether differences among people in the reducing power of the digestion medium cause variation in the amount of iron absorbed, and also whether more iron is absorbed from foods ingested in the morning.

SUMMARY

Saliva collected in both morning and afternoon from four women was incubated with ferric chloride alone and also with ferric chloride and unenriched bread. More iron was reduced by the salivas collected in the morning than by those collected in the afternoon. With ferric chloride alone the reduction was usually less than 5 per cent. The levels of reduction were characteristic of the individual. When bread was added, reductions with the morning salivas ranged from 22.3 to 46.9 per cent and with afternoon salivas from 16.7 to 28.9 per cent.

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The Peroxide-Erythrocyte Hemolysis Test

Experiences in Patients with Cirrhosis, Jaundice, and Polyneuritis

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SERUM tocopherol concentrations lower than normal have been described in patients with malnutrition and malabsorption of fat,[1,2] cirrhosis,[3,4] hyperthyroidism,[5] and in newborn infants.[6] Nevertheless, no human counterpart to vitamin E deficiency in animals has been demonstrated.

The role of vitamin E in preventing hemorrhagic necrosis of the liver induced by deficient diet in animals is well recognized,[7,8] and hepatic abnormalities have been described in animals on deficient diets prior to the development of massive necrosis.[9] These may include karyolysis, karyorrhexis, mitosis, hemorrhage, and the development of refractile eosinophilic cytoplasmic granules. These lesions in some ways are like the "alcoholic hyalin" and necrosis described in the livers of alcoholics with acute hepatic decompensation,[10,11] suggesting that the state of vitamin E nutrition of these patients should be investigated. This was done with a red blood cell hemolysis test, using dilute hydrogen peroxide, which has been correlated with serum α-tocopherol levels in animals,[12] infants and children,[13] and patients with malabsorption of fat.[13,14]

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MATERIALS

Hemolysis tests were performed on blood from 52 patients hospitalized on the wards of the Boston City Hospital. This group included 42 patients with alcoholic cirrhosis, one with "postnecrotic" cirrhosis, four without clinical evidence of liver disease but with symptoms of acute alcohol withdrawal, three with severe malnutrition, one with hyperthyroid myopathy, and one with diabetic polyneuritis and hepatomegaly. Diagnosis of the liver disease was substantiated by autopsy in seven instances and by liver biopsy in nine. Twenty-three patients had clinical icterus (bilirubin above 2.0 mg per 100 ml or icterus index above 20). The ages ranged from 27 to 72 years among the 17 females and 35 males. The patients, selected from those seen in consultation, were chosen to represent chronic and acute cirrhosis, undernutrition, and peripheral neuritis. Three patients with increased hemolysis were followed with serial tests.

METHODS

Erythrocyte sensitivity to hemolysis by dilute hydrogen peroxide was tested using the modification of Horwitt *et al.*,[15] which is similar to the method of Gordon *et al.*[13] and of Rose and György.[12] Variations from this modification included the use of 50 ml boiling flasks in a Seligson-type rotator to agitate the red cells consistently during incubation at 37°C for

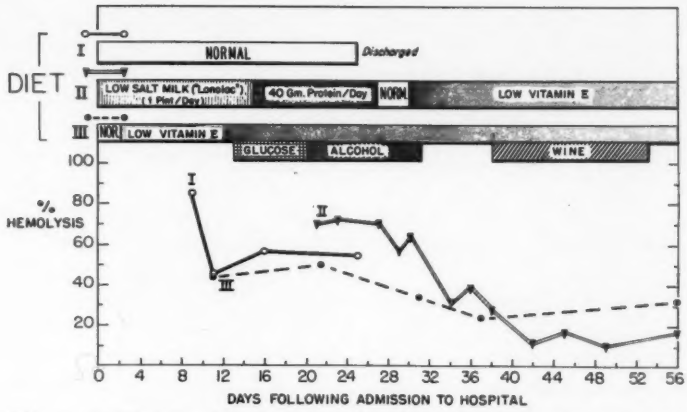

Fig. 1. Erythrocyte hemolysis test following feeding in three alcoholic patients with cirrhosis.

three hours, and the use of 1.0 ml of blood rather than 0.2 ml. Tests were done in triplicate, with error of duplicate samples usually less than 5 per cent for values over 10 per cent hemolysis. Hemolysis of 50 per cent or more has been considered significantly positive when correlated with tocopherol concentration,[13,15] and we also have used this criteria. Eight tests performed initially on ambulatory normal individuals uniformly gave results of less than 5 per cent hemolysis, while umbilical cord blood obtained at the time of delivery from a 16-year-old Negro with a normal, full-term, spontaneous delivery had 34 per cent hemolysis. Cells from normal individuals used concurrently with patients' cells consistently revealed less than 5 per cent hemolysis.

Two patients were given measured diets on which the α-tocopherol intake was calculated using standard tables.[16] Creatine excretion in the urine was measured in one of these patients using the method of Folin.[17] Fat absorption was measured in two patients using oleic acid labeled with I^{131} as described below.[18]

RESULTS

Two of 52 patients had a positive test; that is, red blood cell hemolysis greater than 50 per cent (Table I). There was, however, no definite correlation of erythrocyte hemolysis with the presence or absence of jaundice. The four patients with alcoholic withdrawal symptoms, and three of four with severe malnutrition without cirrhosis, showed less than 10 per cent hemolysis.

Specimens of liver from 16 patients obtained at autopsy or biopsy and stained with hematoxylin-eosin and with phyloxine-methylene blue were reviewed. They were evaluated for the presence or absence of hyalin in liver cells together with necrosis and polymorphonuclear infiltration and have been correlated with the results of the hemolysis test (see Table I). No clear differentiation is evident. The lack of

TABLE I
Results of Erythrocyte Hemolysis Test in 52 Patients

Diagnosis	Hemolysis test: Under 10%	10%–50%	Over 50%
Clinical			
Cirrhosis			
Nonjaundiced	12	7	0
Jaundiced	10	12	2
Alcohol withdrawal	4	0	0
Undernutrition alone	3	1	0
Diabetes, hepatomegaly	0	1	0
TOTAL	29	21	2
Pathologic[a]			
Cirrhosis			
No "alcoholic hyalin" and necrosis	4	3	0
With "alcoholic hyalin" and necrosis	3	3	1
No cirrhosis	2	0	0
TOTAL	9	6	1

[a] *Pathologic* includes the 16 patients in whom microscopic examination of the liver was possible.

correlation is exemplified by patients with livers showing large amounts of hyalin, extensive necrosis, and fibrosis, whose blood was found to have less than 10 per cent hemolysis. In contrast, the patient whose liver had no hyalin, minimal fibrosis, and severe fatty infiltration had 43 per cent erythrocyte hemolysis. The only liver biopsy in a patient with greater than 50 per cent hemolysis did reveal hyalin, fat, slight necrosis, and cirrhosis.

The presence of severe fatty metamorphosis was not always associated with a positive hemolysis test. One patient with an acute fatal illness suggestive of vitamin E deficiency as seen in animals had extensive hepatic fat with massive central lobular hemorrhagic necrosis, masses of hyalin material in liver cells, and intra-alveolar pulmonary hemorrhage; however, the hemolysis test was less than 10 per cent. Thus, we were unable to demonstrate a correlation between the presence in the liver of "alcoholic hyalin" and necrosis or fatty change and a positive hemolysis test.

The three patients with hemolysis tests above 45 per cent were followed with serial tests. Patient 1 was offered a normal diet, but the amount consumed was not recorded. The Boston City Hospital normal diet was estimated to contain about 25 mg total tocopherol and 17 mg α-tocopherol. Patients 2 and 3 each had a short period of three to four days when a normal diet was offered and then received a measured diet estimated to contain 40 g protein, 6 to 8 mg of total tocopherol, and 4 to 5 mg of α-tocopherol daily (Fig. 1). Patient 3 in addition received a Dexin*-grapefruit juice drink for which was substituted an alcohol grapefruit juice drink (33 g of alcohol every six hours) in isocaloric amounts after a suitable control period. Later, port wine equivalent to 33 g alcohol every six hours was substituted. It can be seen from Figure 1 that these measures had no effect in preventing the return of the hemolysis test toward normal. Urine creatine excretion measured in Patient 2 revealed between 10 and 25 mg creatine excreted on the fourth, fifth, and seventh days after receiving a house diet for 4 days. Thereafter, there was no creatinuria on repeated determinations. Fat absorption was estimated by measuring serum radioactivity four hours after oral ingestion of approximately 25 μc of I^{131}-labeled triolein given in a mixture of peanut oil, water, and Tween 80.[18] In Patients 1 and 2 there was 16.7 and 8.75 per cent, respectively, of administered radioactivity in the calculated plasma volume at four hours, compared to the normal value of 10 to 15 per cent. There was no evidence of fluid retention at this time.

In reviewing the records of Patients 1 and 2, who had 85 and 70 per cent hemolysis, respectively, certain similarities were noted. Both were severely alcoholic males with long histories of excessive whiskey and beer intake and poor diets. Each had suffered progressive muscular weakness of nine months to one year's duration, with increasing severity in the one to two weeks prior to admission which had confined each to bed rest at home. Delirium on admission with memory loss and history of weight loss were present in both. On examination they were extremely undernourished and dehydrated and had mild jaundice (serum bilirubin 2.9 and 3.4 mg per 100 ml, respectively), slightly enlarged livers, and ankle edema. There were signs of probable vitamin deficiencies in each. Patient 1 had nystagmus prior to thiamine administration, and Patient 2 had a smooth red tongue and perifollicular hemorrhages and corkscrew hairs over the thigh suggesting scurvy. Mild congestive heart failure was present in Patient 1 with a blood pressure of 78/62 mm Hg, while Patient 2 had severe congestive heart failure with a blood pressure of 80/65 mm Hg and was suspected of having beriberi heart disease, although this was not definitely established. Severe muscular wasting and signs compatible with marked nutritional polyneuropathy were present in both, while Patient 2 had evidence suggesting spinal cord involvement as well. Laboratory evidence of acute hepatic dysfunction was present, and blood studies revealed hematocrits of 45 and 36 per cent, respectively, with moderately hypochromic, normocytic cells, some macrocytes, marked

* Dexin, a partially hydrolyzed starch, produced by Burroughs Wellcome Co., Tuckahoe, New York.

anisocytosis, and target cells. The course was one of gradual improvement following intensified and diverse therapies; however, no α-tocopherol other than in food, as described earlier, was given. Improvement in the polyneuropathy and muscular weakness took several months.

Patient 3, with an erythrocyte hemolysis test of 44 per cent, was a chronic alcoholic who had continued to eat moderately well and had retained his job. His history was of fatigue, weakness, and weight loss of several months' duration. On admission he had clinical and laboratory evidence suggestive of severe folic acid deficiency: hemoglobin 6.2 g per 100 ml, hematocrit 20 per cent, erythrocyte count 130 million per cu mm, mean cell volume 155, mean corpuscular hemoglobin concentration 31, reticulocytes 1.8 per cent, serum vitamin B_{12} content 1900 $\mu\mu$g per ml, leukocyte count 6,800 per cu mm (71 per cent polymorphonuclear); bone marrow was hyperplastic with megaloblasts and atypical white blood cell precursors. There was jaundice (bilirubin 3.4 mg per 100 ml) with an enlarged liver, a palpable spleen tip, and slight but definite ascites. He was obese and did not appear as severely undernourished as the other two patients. Neurologic examination revealed depression of deep tendon reflexes bilaterally with some evidence of peripheral neuritis, but not as severe as in Patients 1 and 2. He improved on a low-folic acid, low-vitamin E diet; however, he received a normal diet for a three-day period prior to the measured diet (see Fig. 1). One month after admission, laboratory data were: hemoglobin 13.3 g per 100 ml, hematocrit 44.3 per cent, erythrocyte count 4.01 million per cu mm, reticulocytes 0.3 per cent, mean cell volume 111, mean corpuscular hemoglobin concentration 30, leukocyte count 8,000 per cu mm (43 per cent polymorphonuclear).

In view of the similarity of these cases, other cases of nutritional polyneuropathy were sought and tested. The results are shown in Table II and indicate a somewhat higher degree of hemolysis than in Table I, although patients in Table II are also included in Table I. There was no direct correlation between clinical estimate of severity of peripheral neuropathy and results of the hemolysis test. Two nonalcoholic patients were studied, one of which, with hyperthyroid myopathy, had less than 10 per cent hemolysis, while the other, with diabetic polyneuropathy, had 28 per cent hemolysis. No tests were performed to determine whether myopathy existed in addition to neuropathy in these patients.

TABLE II

Results of Erythrocyte Hemolysis Test in 14 Patients[a] Who Had Clinical Evidence of Polyneuropathy

Polyneuropathy	Hemolysis test		
	Under 10%	10%–50%	Over 50%
Cirrhosis			
Nonjaundiced	1	4	0
Jaundiced	2	3	2
Other	1	1	0
TOTAL	4	8	2

[a] These patients are included in Table I.

DISCUSSION

The results presented here indicate no definite abnormality of the erythrocyte hemolysis test in patients with cirrhosis. The slight abnormality seen in some patients with cirrhosis may be due to deficient fat absorption,[18] as low serum tocopherol levels with positive hemolysis tests have been described in patients with malabsorption of fat.[1,14,19] Klatskin,[20] however, has reported normal α-tocopherol absorption in a group of 11 hospitalized patients with cirrhosis and suggests that decreased intake may account for low α-tocopherol levels. Measurement of fat absorption in the two patients with highest hemolysis test suggested a mild defect in one patient only.

No correlation of erythrocyte hemolysis was found with the presence or absence of jaundice or with pathologic evidence of "alcoholic hyalin" and necrosis of the liver. This is consistent with previous studies of cirrhosis which have indicated lower than normal mean blood tocopherol levels in cirrhosis and no correlation with degree of hepatic dysfunction, type of liver disease, serum bilirubin levels, or serum cholesterol levels.[3,4]

The unexpected positive hemolysis tests (over 50 per cent hemolysis) found in two patients with only mild cirrhosis and with similar

illnesses manifesting delirium, muscular wasting, severe polyneuropathy, and cardiac failure suggested vitamin E deficiency. Naturally occurring vitamin E deficiency in swine may be associated with sudden onset of coma and death, hepatic necrosis, voluntary muscle degeneration, pulmonary edema and pulmonary hemorrhage.[21] Vitamin E-deficient diets or diets containing vitamin E antagonists* in swine and rats may produce severe liver necrosis, muscular dystrophy, ceroid pigment in the liver cells, and demyelinization of peripheral and spinal nerves.[22–26] Monkeys deficient in vitamin E have been observed to have abnormal cardiac function with electrocardiographic abnormalities similar to those found in thiamine-deficient monkeys.[27] The positive hemolysis tests in these two patients and the presence of similar lesions in vitamin E-deficient animals only suggests but does not prove a deficiency of α-tocopherol in the etiology of their illness.

The gradual return of the hemolysis tests to normal following feeding minimal amounts of α-tocopherol in food indicates either that only small amounts of vitamin E are needed to produce a normal test or that other factors may affect the test. Horwitt and associates[15] fed 15 mg tocopherol a day to a subject previously depleted by a 2 mg tocopherol diet and noted a gradual rise in serum tocopherol with a fall in hemolysis test over several months. Thus, it would seem that between 2 and 15 mg daily of α-tocopherol were needed for the presence of a normal hemolysis test. Our results suggest that three to four days of normal diet followed by only 5 mg of α-tocopherol daily may reverse a positive hemolysis test.

It should be emphasized that the hemolysis test may not be specific for α-tocopherol and that it does not completely parallel blood α-tocopherol concentrations. Other factors such as red cell-catalase content may affect the test.[28] It is possible that extreme undernutrition may affect the hemolysis test in a nonspecific manner; however, our patients with severe undernutrition alone did not show marked abnormalities. Although there is no direct correlation, serum α-tocopherol levels of less than 0.5 mg per 100 ml have been associated with positive hemolysis tests.[15,29] Also, humans on experimental 2 mg α-tocopherol diets develop a gradual decrease in serum α-tocopherol with an increase in the hemolysis test.[15] Recently, a case of biliary cirrhosis has been described with low blood α-tocopherol levels, a positive hemolysis test and creatinuria.[30] These laboratory abnormalities improved with administration of large amounts of α-tocopherol. There have been other reports suggestive of human vitamin E deficiency;[14,22,31,32] however, in none of these reports is there evidence of a definite etiologic relationship between lack of vitamin E and a clinical syndrome.

Alcoholic peripheral polyneuritis has been associated with vitamin B deficiency for many years.[33,34] The results reported here in the two patients with marked abnormalities of hemolysis test and the tendency toward increased hemolysis in patients with nutritional polyneuropathy would suggest further investigation of vitamin E in this circumstance.

SUMMARY

Red blood cell sensitivity to hemolysis with hydrogen peroxide has been determined in 52 patients, 49 of whom had cirrhosis.

No definite correlation was found with the severity of cirrhosis, the presence of jaundice, or the presence of "alcoholic hyalin" and necrosis of the liver.

Only two patients had strongly positive tests (greater than 50 per cent hemolysis), and both had multivitamin deficiency with mild cirrhosis and severe polyneuropathy suggesting but not proving vitamin E deficiency in these two patients.

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* Substances reported to antagonize vitamin E include tri-*o*-cresyl phosphate (ginger paralysis), carbon tetrachloride, sulfonamides, pyridine, sodium sulfite, and unsaturated fatty acids.[22]

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Science is always wrong. It never solves a problem without creating ten more.—George Bernard Shaw

Experimental Lathyrism

Review of The Literature

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INVESTIGATION of the metabolism of connective tissue by pathologists, endocrinologists, biochemists and others has been recently centered upon experimental lathyrism. The main reason for this is that the skeletal aberrations produced by feeding rats with the seeds of the sweet pea, *Lathyrus odoratus*, are similar, if not identical, with certain diseases of the human skeletal system, for which the etiology is unknown.

With reference to *Lathyrus odoratus*, a survey of the large literature demonstrates the confusion and ignorance that still exist in this area. The object of this review is to systematize and correlate the observations of the past century.

GENERAL PATHOLOGY OF LATHYRISM

Lathyrism is essentially a neurologic and skeletal disease caused by ingesting certain legumes, particularly *Lathyrus odoratus*.

In 1886 Schuchardt[1] in the first comprehensive review of the literature (1784–86), described the manifestations of lathyrism to be a symptom complex with spinal paralysis.

Stockman[2] in 1917 reported lathyrism in monkeys and rabbits fed the lathyrus peas. He observed that monkeys developed spasmodic attacks at irregular intervals, followed by paralysis of their hind limbs. Death was due to a failure of the respiratory muscles. In experiments on rabbits, a transient, slight spasmodic condition of the legs occurred. In guinea pigs he noted tremors, spasticity and weakness of the legs with mortality in all the experimental animals in 8 to 35 days. He attributed the lethal action to the presence of a toxin, which altered the assimilation of the proteins of the lathyrus peas.

The toxic principle in lathyrism according to Stockman and others was a very small amount of an alkaloid which produces paralysis when given to frogs, monkeys, and mice.

The literature presents controversial reports on the production of lathyrism in animals. Howard and co-workers[3] in 1923 thought that different investigators found discrepancies in the production of lathyrism because of an admixture of weeds in the samples of lathyrus peas consumed. Investigators who failed to produce lathyrism had a large amount of weeds and a small concentration of Lathyrus seeds.

In 1927 McCarrison[4] produced this syndrome in rats with lathyrus peas as their only food. Zagami,[5] however, failed to produce symptoms of lathyrism in rats when he fed them a diet made up entirely of lathyrus peas for 150 days. He reported a decrease in rate of gain of weight, a retardation in sexual development and a decrease in calcification of the skeleton. The findings can be readily explained by the fact that the seeds, as sole diet, are deficient in various nutritive elements.

Geiger and co-workers[6] in 1933 first reported osseous changes in the rat with lathyrism. The spinal column in every case showed extreme curvature in the thoracic region. They also noted scoliosis and hernia in white rats fed a diet containing 50 per cent sweet peas. The symptoms were lameness, spinal and sternal curvature, enlargement of the costochondral junction, and malformations with an abnormal red color of the long bones. Calcification was interfered with in young animals. The redness

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of the bones was associated with a slight polycythemia and high hemoglobin content of the blood. The toxic factor was extractable from peas by the use of boiling water.

The young animals received neither cod liver oil, cod liver oil concentrate, nor dried yeast as protection against toxicity of the sweet peas. The adult animals, however, were protected to some extent by the addition of 2 per cent cod liver oil to the ration. The sweet peas used were a better source of vitamin A than any other seeds previously studied, since normal growth was obtained on a diet which contained 5 per cent of sweet peas as the only source of vitamin A.

The sternum frequently showed deformities;[6] the ribs were misshapen, and the costochondral junctions were enlarged, with angulation in some rats. The femur and humerus were deformed, the upper end of the femur was broadened, and there were rough areas on either side at the points of attachment of the muscles. The humerus was thickened and had similar roughened areas. The weights of the femur and humerus were 33 and 26 per cent less than in the control animals.

The ash content of the bones of the adult fell within normal limits. In the young animals the amount of ash was decreased. The serum calcium and inorganic phosphorus of adult animals were within normal limits.

It is of interest that there was a decrease in the ash content of the bones of young experimental animals, whereas the incisors of rats showed a slight increase in the ash content.

Figure 1 illustrates the spectacular skeletal changes that take place in weanling rats fed a diet containing 50 per cent sweet peas for 21 days. The bones are hyperemic, and hemorrhages are noted in the muscle and in connective tissue immediately adjoining the roughened areas of exostoses on the humerus and femur. The appearance of the bones suggested a possible increased hematopoietic activity. Three-fourths of the animals had a high hemoglobin level with a slightly elevated erythrocyte count.

The spleen was somewhat smaller in animals receiving the diet containing 50 per cent sweet peas than in control animals fed a normal

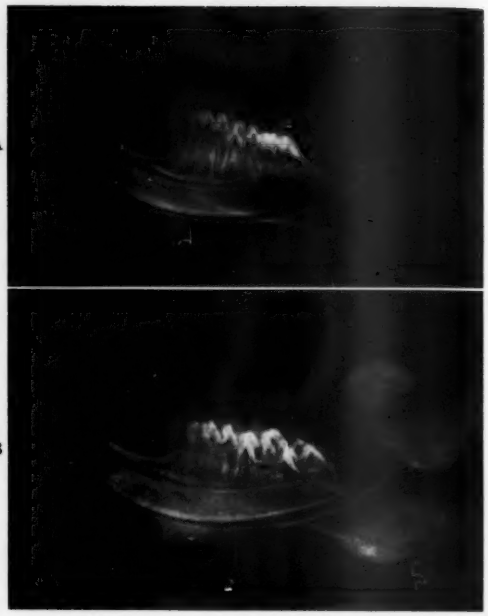

Fig. 1. (A) Roentgenogram of the mandible of a control rat 43 days of age. (B) Roentgenogram of the mandible from a rat receiving 50 per cent sweet pea for 21 days.

diet. Lameness was evident after 12 weeks in animals receiving 50 per cent sweet peas with no vitamin supplement.

It was also noted that a watery extract of the lathyrus peas had a toxic action on the brain and spinal cord.[7]

Cases of primary lateral sclerosis, indistinguishable from lathyrism, were reported by Minchin[8] in 1940. Other workers,[9] however, failed to produce any untoward symptoms in rats fed diets containing 50 per cent sweet peas. But Turney and his colleagues[10] found that diets containing 10 per cent lathyrus seeds caused reproductive failure in rats, and feeding alpha-tocopherol in unspecified amounts did not negate this effect. They reported that lathyrus seeds prevented rats from completing pregnancy, but they did not completely describe the nature of the disturbance. Spontaneous lathyrism has been reported to occur in livestock grazing in fields containing lathyrus peas.[11]

Although in 1947 Denny-Brown[12] questioned whether lathyrism in human beings is the same

as that produced in rats by feeding them the seed of flowering sweet peas, Lewis and co-workers[9] reported that changes due to lathyrism in the femurs of rats were similar to those in human osteomalacia. In the rats irregularities of the proximal third of the femur occurred with thickening of the cortices, subperiosteal calcification and multiple deformities near the end of the shaft. Osteoporosis was present in the long bones. The most striking changes were in the knee joints; there was also fragmentation of the epiphysis of the tibia, femur and patella. Marginal sclerosis was present and some evidence suggesting hemarthrosis. The changes in the knee joints might be compared to those in Charcot's disease in man, a disorder of neurotrophic origin.

Lewis and associates[9] also reported that lathyrus peas are deficient in certain essential amino acids, particularly methionine. However, the lesions produced by the sweet peas are not solely due to a protein deficiency. Adding 10 per cent casein did not prevent or delay the onset of lathyrism in rats. It was postulated that the lameness of the lower extremities is due to compression of the cord at the level of the kyphoscoliosis.[9]

In my laboratory I have been successful in preventing the formation of bony exostoses at sites of muscle insertions by the addition of 40 per cent casein to a 30 per cent sweet pea diet.

Rats on diets containing lathyrus peas developed a shuffling gait within ten days, which gradually progressed to complete paralysis of

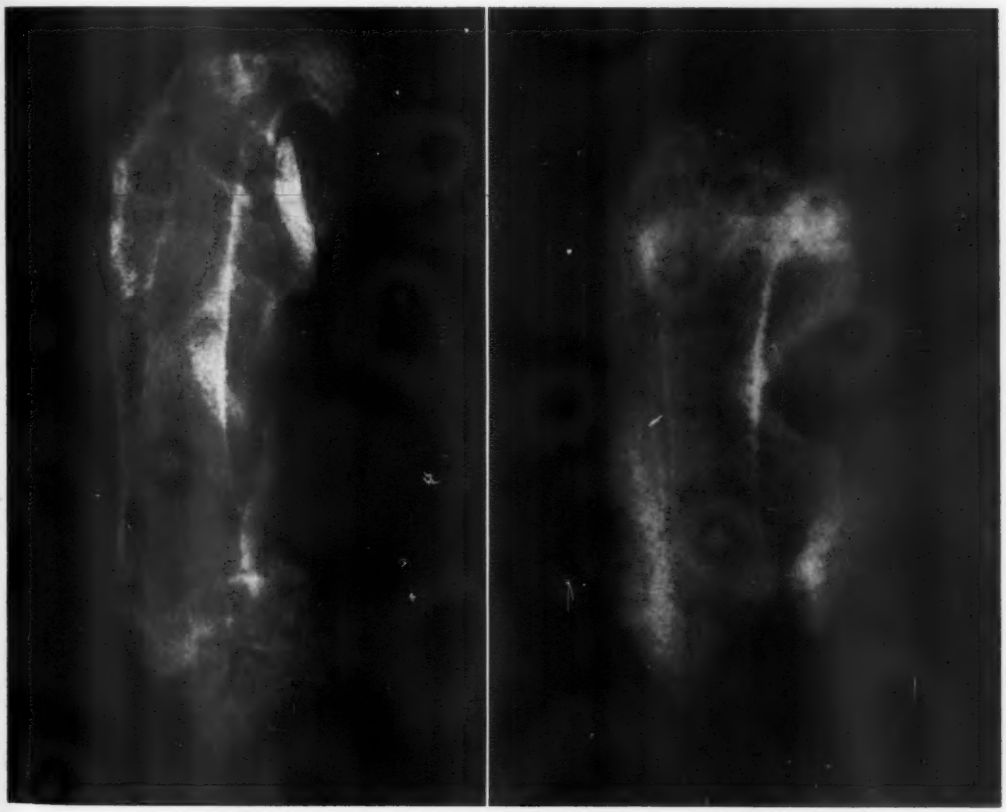

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Fig. 1 (*Cont.*) (C) Roentgenogram of femur from rat receiving 50 per cent sweet pea for 21 days. (D) Roentgenogram of femur from rat receiving 0.8 per cent β-amino-propionitrile for 2 weeks.

the hind quarters by the end of the 30-day period.[13] Other symptoms were curvature of the spine, exostoses of the long bones, incontinence and emaciation. No deaths occurred. On autopsy the exostoses were easily apparent, the bones discolored, and the epiphyses of the long bones greatly enlarged. The tibias developed a club-like appearance. Muscular atrophy was apparent. When paralyzed animals were returned to stock feed and given a chance to recover, only one in a large group recovered the use of its legs. Koziewska[14] also noted spastic paraplegia in animals which had ingested seeds of the lathyrus peas.

Vivanco and co-workers[15] proposed the term "odoratism" referring to the lathyrism resulting from ingestion of *Lathyrus odoratus* (sweet pea). In their experiments with rats fed sweet peas, the resulting syndrome was characterized by paralysis of hind limbs, retention of urine, and kyphosis.

They found lameness of the hind legs, scoliosis, and periosteal ossifications in the femurs of rats fed a diet containing large amounts of sweet pea meal. Before scoliosis appeared, decompression laminectomies were performed without noticeable effects on the lameness. It was postulated that the sweet pea has a toxic action on the spinal cord and bone.[15]

The comparative data of Schulert and Lewis[16] are the best for removing doubt that the toxicity in lathyrism is associated with the presence of a definite toxic material within the seeds. Osteoporosis resulting from lathyrism, they showed, is due to an organic toxic substance in seeds of the plant.

I believe this osteoporosis is in part due to disuse atrophy because of the inactivity of these animals when the periosteal detachments occurred and in part due to excessive osteoclastic resorption of bone.

The gross manifestation of lathyrism is a skeletal change that affects the mandibles of the experimental rat.[17] Spectacular skeletal changes may take place in the mandibles of rats on sweet pea diets. When Dasler[17] fed a 50 per cent sweet pea diet to weanling rats, exostoses developed on the ventral and lateral aspects of the mandible. The exostoses were palpable in all rats at the end of one week and became progressively worse. A disturbance in collagen metabolism or connective tissue metabolism was postulated.

In 1954 Dasler[18] called attention to a notching of the incisors in growing rats fed sweet peas. He suggested this notching is mechanical in origin, in that the overgrowth of bone in the proximal portions of the mandible probably limits the range of movement of the jaw and thus interferes with the normal attrition of the incisor. He concluded that rats fed diets of 50 per cent sweet peas for three weeks showed decreases in femur ash and increases in incisor ash when compared with rats fed control diets ad libitum, or by the paired feeding technic. There is no conclusive evidence that a disturbance in calcium and phosphorus metabolism is involved in the development of this disease, but the effects of lathyrism on the mineralization of the skeleton are secondary to disturbances in the metabolism of connective tissue, or of a connective tissue component.

These experiments suggest that calcium deficiency as a factor does not merit too serious consideration; however, further biochemical data on this point should be obtained.

I have observed that a shagginess of the fur occurs with loss of its normal glossy sheen and a tendency to alopecia. This is perhaps explainable by the fact that nutrients are available to the epidermis solely by way of the connective tissue and its vessels so that the epidermis fails to grow when lacking a functional mesenchymal pulp.

More recently, Dasler[19–21] reported that hemoglobin levels and serum alkaline phosphatase levels appeared to depend more upon nontoxic variations in the diet and upon the nutritional status of the growing rat than upon the toxicity of the diet. An edible pea diet, he concluded, is a very inadequate control for a ration containing *Lathyrus odoratus* when the levels of certain constituents in the blood are to be investigated.

Inasmuch as Dasler[17] had found that serum alkaline phosphatase was not appreciably altered in lathyrus-fed rats, derangement of this enzyme mechanism was thus absolved of any major responsibility in the deforming process.

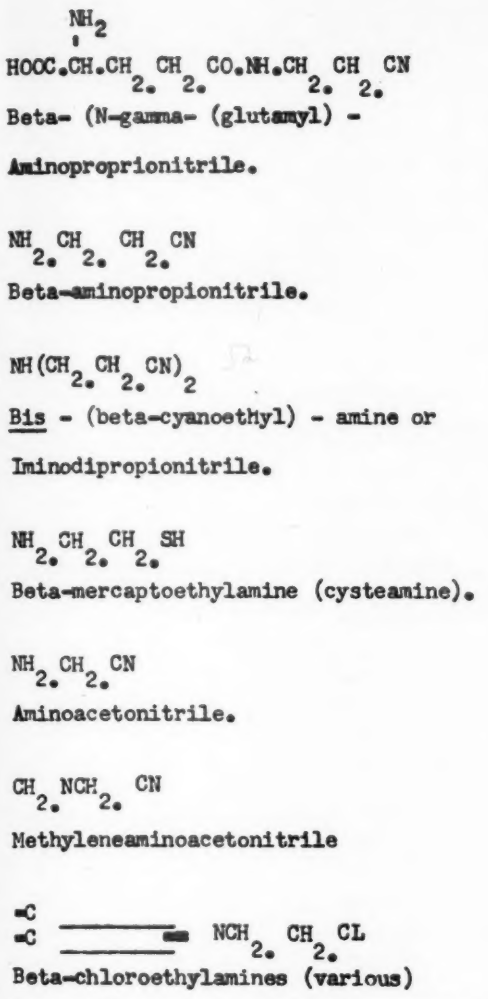

Fig. 2. Substances causing skeletal changes typical of lathyrism.

The adrenal weights in male rats suffering from lathyrism are significantly greater than those of control animals of the same age. This is true whether the control animals are pair-fed with the experimental group or whether they receive the control diet ad libitum. Adrenal weights in female rats suffering from lathyrism are not significantly different from adrenal weights of control animals of the same age. However, adrenal weights per unit of body weight are significantly higher for both female and male rats suffering from lathyrism than for control animals. The effect of lathyrism on the adrenals may be secondary to a disturbance in collagen metabolism, according to Dasler.[17]

Churchill and co-workers[22] found that rats fed the toxic lathyrus factor developed aortic aneurysms, edema, and medial hemorrhage. The factor was also associated with increased metachromasia and periodic acid-Schiff (PAS) positive material. The investigators noted at least two polysaccharides undergoing this increase; the most pronounced changes were in association with the metachromatic substances. The polysaccharide demonstrated in these aortas by the degree of metachromasia would seem to conform most closely to criteria established for chondroitin sulfate B. In the present state of our knowledge, it is not improbable that the degree of metachromasia is directly or indirectly indicative of the degree of polymerization of the chondroitin sulfate component of the ground substance.

Mucopolysaccharide alteration in the rat aortas was frequently associated with degeneration of elastic fibers. The dissecting aneurysms of the aorta which occur in rats suffering from odoratism are grossly and microscopically similar to cases of medial degeneration of the aorta in humans.

The fact that lesions localize in the skeleton and aorta must have some significance, so also does the constant production of an intercellular material which is strongly metachromatic but PAS-negative. This combination of site and staining reaction identifies the material as chondroitin sulfate. Thus one may conclude that there is an important connection between the lathyrus factor and the sulfated mucopolysaccharides.

CLINICAL SYMPTOMS

It has been noted that spastic paraplegia in malnourished prisoners of war was similar to lathyrism.[50]

Stearns and Ponseti[52] found that protein metabolism is at fault in children with idiopathic scoliosis. They reported many points of similarity between roentgenologic characteristics of scoliosis in rats with lathyrism and idiopathic scoliosis.

On the other hand, from different areas in southern India, Gopalan[51] reported 61 sporadic cases indistinguishable from lathyrism, yet unrelated to the eating of lathyrus peas.

AMINOPROPIONITRILE COMPOUNDS

Beta-aminopropionitrile is the teratogenic agent of the seeds of *Lathyrus odoratus*.[22] It produces dislocation of joints and loosening of the intersegmental septa in amphibians and bends the femur in chick embryos. The minimal teratogenic concentration for *Xenopus laevis* larvae is 0.5 ml/liter; the minimal dose for chick embryos is 1 ml/liter. The effects are highly tissue-specific but not species-specific. The available evidence suggests that the presence of this compound interferes with a single morphogenic process during differentiation.

Formulae for the substances which give rise to skeletal lesions resembling those found in lathyrism are shown in Figure 2.

Stamler[24] reported that when added to the diet of the pregnant rat, *Lathyrus odoratus* peas and certain aminonitrile compounds chemically related to the active extract of the pea caused death of the fetal rat later in intrauterine life. Death was associated with poor development of the skeleton and other mesodermal tissues and commonly resulted from rupture of the thoracic aorta at or near the time of birth. No harmful effects on the fetus were demonstrated by feeding these substances to the pregnant female before the seventeenth day of gestation. *Lathyrus odoratus* peas in a 50 per cent dietary concentration did not affect fertility of the adult male or female rat, and males maintained on the diet for as long as ten months showed no histologic evidence of testicular atrophy. No toxic substance was demonstrated in the milk of nursing females on the pea diet. The feeding procedure employing pregnant female rats was a reasonably accurate and sensitive method for assaying the toxicity of aminonitriles. Aminoacetonitrile was the most toxic of the compounds tested.

Levy and Goodman[25] found that *Amblystoma punctatum* embryos reared in a 1 mg/100 ml aqueous solution of the crystals of *Lathyrus odoratus* developed tumors of the notochord. They discussed two possible mechanisms of pathogenesis of these lesions. These tumors could arise as a consequence either of a focal degeneration of the notochord sheath, leading to secondary proliferative ecchordoses or prolapses, or of a direct stimulation to proliferation of the notochord cells. They found deformities of the mandible and forelimbs of *Amblystoma punctatum* when fed the crystalline lathyrus factor. The effects of the lathyrus toxin conformed to those of other investigators, i.e., an effect on the mesodermal, ligamentous, fascial, cartilagenous, and bony structures. It was postulated that focal degeneration or aplastic changes of the chordal sheath are the primary lesions in lathyrus-intoxicated larvae. These are followed as a secondary event by ecchordoses or prolapses of the chordal tissue with resultant excessive proliferations.

Gershon-Cohen and McClendon[26] noted that roentgenography is a very effective means of studying progressive osteoporosis due to lathyrism in rats. This type of osteoporosis is not appreciably influenced by adding brown rock phosphate supplements to the diet. The investigators believed that the decalcification accompanying lathyrism may be a direct effect of the toxin on bony structures, but the generalized spastic contractures also suggest an indirect effect through the nervous system, resulting in muscle spasm and atrophy of disuse in the bones. Other bone abnormalities found were hypertrophy at the attachments of muscles, tearing of the periosteum, and herniation of the intervertebral disks.

HISTOPATHOLOGY OF LATHYRISM

In 1954 Dasler[17,19] described the characteristic findings in rats fed lathyrus peas. The spine shows the same severe changes that are seen in the long bones. The sharply localized collapse of the centra bespeaks an early decalcification which has resulted in so severe a compression of the spinal chord that there is adequate explanation of the paralysis of the extremities. There is much new formation of connective tissue and cartilage and also periosteal hemorrhage. The proliferation of connective tissue extends into the neighboring muscle.

The bone marrow after decalcification is in

part fatty, and there is much less hematopoiesis than in the control animals. A new formation of bone is produced upon the original cortex, and a sclerotic layer has developed in the periosteum.

These phenomena are obviously reactive, but what stimulus provokes them is still a controversial point. The stimulus is not hemorrhage, since no hemosiderin has been apparent. It is possible that the stimulus is the excessive ground substance itself. Epiphyseal lines are widened, particularly at the upper end of the femur. Ossification is delayed, as in rickets.

Ponseti and Baird[27] reported that white rats fed a diet containing 50 per cent *Lathyrus odoratus* seeds all developed kyphoscoliosis. The scoliosis apparently resulted from osteoporosis and collapse of several vertebrae. Paraplegia developed in two rats with very severe kyphoscoliosis and cord compression. Aneurysms of the thoracic aorta were seen in six of the eight animals which died intercurrently. The aneurysms developed when the vertebral deformity was still mild. No toxic lesion was demonstrated in the liver, kidney, or other organs. These investigators said that *Lathyrus odoratus* seeds appear to contain a toxic factor which affects the formation of organic bone matrix, the aorta, and possibly other mesodermal structures.

It appears reasonable to point to a possible relation between these experimentally produced aneurysms and the cardiovascular lesions commonly seen in arachnodactyly (Marfan's syndrome).

In 1954 it was reported[28] that diets containing these seeds produced a hitherto unrecognized lesion in the epiphyseal plates of rats. These lesions are very wide, the cartilage matrix appears to lose cohesion, and the cartilage cells are grouped in clusters. The same diets produce loosening and detachments of the tendinous and ligamentous insertions.

The following skeletal conditions developed in the experimental animals: epiphyseal slippings, metaphyseal fibrous defects, kyphoscoliosis, thoracic deformities, detachments of the tibial tuberosity, subluxations and dislocations of the shoulder, diastasis of the sacroiliac joints, degeneration of the intervertebral disks, disk herniations, Legg-Perthes-like disease of the femoral head, and valgus of the forepaws. Ponseti has also demonstrated a similar disruption of the epiphyseal plate in Legg-Perthes, disease. All the experimental animals had extensive areas of periosteal new bone formation after detachment of the periosteum.

Degenerative arthritis was observed in rats fed lathyrus peas for several months. Two lesions developed concomitantly, degeneration of the joint cartilage and loosening of the capsular and ligamentous insertions.

Bone lesions resembling those seen in Paget's disease were observed in small groups of older rats. Dissecting aneurysms of the aorta and abdominal and inguinal hernias were observed in many rats. The collagen fibers appeared to be normal on electron microscopic examination. The authors[28] surmised that these lesions were due to defective formation or excessive destruction of the chondroitin sulfate of the ground substance.

The point of initiation in the pathogenesis of lathyrism is doubtful. It is unlikely to affect ground substance by a chemical reaction, but it may act as an enzyme poison interfering in some way with the maintenance or elaboration of connective tissue materials.

Again in 1954, Ponseti and Shepard[29] published necropsy findings on animals fed sweet peas. The significant observations in the skeleton and aorta were confirmed. The thoracic and abdominal organs appeared normal except for underdeveloped testes. Five rats, which died spontaneously five to nine weeks after being put on a pea meal diet, had massive bilateral hemothorax, and one rat had hemopericardium. At necropsy, rats with paraplegia demonstrated cord compression at the site of the very severe thoracic kyphoscoliosis.

ETIOLOGY OF LATHYRISM

As early as 500 B.C., Hippocrates observed that lathyrism was due to a protracted and monotonous diet of certain peas but that the toxin responsible was not identified.

In 1920 Dilling[30] extracted an alkaloid from the seeds of the lathyrus peas. On inoculation into animals, it produced the symptoms of

lathyrism. A substance resembling a water-soluble amine was obtained from lathyrus peas in 1922 by Acton and Chopra,[31] who showed that injections of it produced lathyrism in ducks and monkeys. These investigators reported paralysis in the hind legs of monkeys, guinea pigs, rats, and mice with the pure hydrochloride of the amine obtained from peas.

In 1924 Anderson and associates[32] suggested that the poisonous effects of ingesting lathyrus peas were due to other seeds found mixed with them. When these seeds were fed to ducks, they caused death. The seeds were reported as containing bases showing alkaloidal properties, of which the investigators isolated three. One of them, divicine, produced characteristic symptoms of lathyrism when injected into guinea pigs.

Young[33] suggested that lathyrism is a deficiency disease due primarily to vitamin A deficiency. If the lathyrus pea constitutes one-third to one-half of the diet for two or three months, it is sufficient to cause the development of the disease. It was also found that a watery extract of lathyrus peas contained phytates, which inhibit the absorption of calcium.[7]

Rudra and colleagues[34] reported that lathyrism is not due to a deficient intake of thiamine; however, the absorption of thiamine may be deficient because of a high serum phosphatase level, which they found in all cases of lathyrism investigated by them. The amount of methionine excreted was not related to the amount of methionine in the sweet pea diet.[35]

However, Rudra and his associates[36–38] found only one-fifth of the normal amount of methionine is excreted in lathyrism. The amount is restored to normal when the patient stops eating the lathyrus peas. According to Rudra[41] khesari, a form of dal* containing little methionine, is often responsible for lathyrism. He suggested that methionine deficiency with other multiple deficiencies may be the cause of lathyrism.

Daniel and co-workers[39] have made it abundantly clear that differences in species of test animals, test conditions, species and strain of peas, and growing conditions all greatly influence the apparent toxicity of the sweet pea.

It was suggested that a toxin elaborated by the mycelia of a fungus symbiotic on lathyrus peas is absorbed into and distributed throughout the plant, including its seeds.

Reviewing 77 cases of lathyrism in human beings in 1950, Rodriguez-Arias[40] found that only 4 patients were female, a ratio in accordance with the usual predominance in human males. He was convinced that lathyrism is a virus infection from contaminated lathyrus peas.

In the past half dozen years, a number of investigators have tried to identify the toxic factor in lathyrism. Rudra[41] claimed that it was selenium. McKay and his associates[42] used rats in assays for the factor and roentgenographic evidence of skeletal deformities as the chief criterion of lathyrus toxicity. A crystalline substance which they isolated produced bony changes exactly similar to those seen in rats fed the toxic meal. Analysis of the purified toxic factor agreed with the formula $C_8H_{12}O_3N_3$.

From lathyrus seeds, Dupuy and Lee[43] isolated a crystalline substance which produced characteristic skeletal lesions. This material is a nitrogen-containing organic compound.

An organic toxic substance isolated from the seeds of the lathyrus peas caused the osteoporosis resulting from lathyrism.[44] The crystalline compound isolated from *Lathyrus odoratus* has been identified as beta-(gamma-L-glutamyl)-aminopropionitrile. This compound is capable of producing the skeletal abnormalities characteristic of lathyrism. Wawzonek and co-workers[45] reported in 1955 that β-aminopropionitrile fed to weanling rats (at a concentration of 0.1, 0.4, and 1.0 per cent in their diet) produced widening and extensive disruption of the epiphyseal plates, widespread periosteal new bone formation, loosening and detachment of the ligamentous and tendinous insertions, degenerative arthritis, and dissecting aneurysm of the aorta. Roentgenograms showed that the epiphyseal plate lesions and periosteal new bone formations were extremely severe in the rats fed β-aminopropionitrile in a 1 per cent

* Dal is a kind of pulse or edible pea, chiefly *Cajanus indicus*, of India.

concentration, severe in rats fed 0.4 per cent, and slight in rats fed 0.1 per cent. Histologically, these lesions appeared to be identical to the lesions in rats fed diets containing 50 per cent *Lathyrus odoratus* (sweet pea) seeds.

Chang and associates[23] reported that when *Xenopus laevis* larvae were fed sweet pea seed, there were dislocations of the joints of the hind legs and loosening of the septa of the metameres of the dorsal musculature. When given at a critical period, about ten days before metamorphosis, β-aminopropionitrile, at a concentration of 1:500,000, produced the lesions within a week. Since the *Xenopus laevis* larvae are so sensitive, they may be used in the bioassay of small amounts of β-aminopropionitrile. This compound will produce all the changes which have been described in rats fed 50 per cent lathyrus odoratus pea meal.[46] None of the supplements fed with BAPN inhibited the development of skeletal deformities. Substituting a methyl or acetyl group into the amino group, or a hydroxy group for the amino group, in BAPN, resulted in a loss of biologic activity.

Unlike BAPN, which principally modified bone development and produced considerable skeletal deformity, β(cyanoethyl)amine exerts an early and pronounced influence on the central nervous system and subsequently produces lesser skeletal alterations. Synthetic β-aminopropionitrile and β-mercaptoethylamine when fed to rats both produced skeletal changes similar to those caused by sweet peas.[21] The mercaptoethylamine was the less effective in producing skeletal changes, although experiments indicated it to be at least as toxic as aminopropionitrile. The glutamyl salt produced typical changes. Aminoacetonitrile also has been reported to produce skeletal lesions typical of lathyrism[45] (see Fig. 2). Although other investigators have implicated selenium as a cause of lathyrism, Robinson[47] in 1955 found that *Lathyrus odoratus* seeds contained only 1 p.p.m. of selenium.

TREATMENT AND PROTECTION AGAINST LATHYRISM

Several dietary factors have been implicated in lathyrism. Mellanby[48] said in 1930 that vitamin A can prevent the detrimental effects of the neurotoxic factor in lathyrus seeds. It can, he suggested, prevent the degenerative change in the spinal cord seen in lathyrism.

Fitzhugh and associates[49] found that a deficiency of vitamin E in rats, induced by feeding them rancid fat, resembles the paralysis of lathyrism. The fact that large supplements of synthetic α-tocopherol gave partial protection indicates the possibility that a relative deficiency of vitamin E may be involved in the development of paralysis. These investigators found it difficult to reconcile the pronounced skeletal changes and the large dosages required for even partial protection with the idea that a simple induced deficiency of vitamin E is at fault. The failure of other antioxidants to confer any protection seemed to indicate that the effect of the tocopherol did not lie in its antioxidant effects in the intestines. It was found that α-tocopherol fed in large doses conferred some protection against the paralysis developed in lathyrism.

Lewis *et al.*[9] were unable to prevent or delay the onset of odoratism by incorporating casein into the experimental diet in levels up to 25 per cent. According to Dasler[19] in 1954, no preventive or curative measures for lathyrism have been devised, although he has had some slight success with high-casein diets. A deficiency of an essential amino acid could not possibly be involved in odoratism, because the animals continue to grow.[20] Further, the symptoms of odoratism are profoundly different than those produced by any known amino-acid deficiency. High levels of gelatin and especially of casein delayed but did not prevent the onset of experimental lathyrism in the rat.

SUMMARY AND CONCLUSIONS

The literature on lathyrism has been reviewed. "Lathyrism" may be produced in experimental animals by feeding *Lathyrus odoratus* seeds. It may likewise be produced experimentally by adding small amounts of β-aminopropionitrile (BAPN) and aminoacetonitrile (AAN) to an otherwise normal diet. It has been stated that sweet pea or BAPN specifically poisons the mesoderm but spares

the ectoderm. In contrast, the ectoderm grows and appears normal, and does not react with the nitrile. The lesions of lathyrism (skeletal lesions, nervous manifestations, and ocular changes) closely resemble certain spontaneous diseases of man. The major questions still to be resolved are: How is the metabolism of connective tissue altered to accentuate the aging of mesodermal tissue that occurs in lathyrism? What can be elucidated concerning the mode of action and the metabolic site at which the "toxin" acts? The answers may clarify the pathogenesis of many spontaneous skeletal diseases in man, including diseases like idiopathic scoliosis, slipped epiphysis, herniation of intervertebral disks, degenerative arthritis, Legg-Perthes' disease, and Paget's disease of bone, which closely parallel experimental lathyrism, in at least some of their manifestations.

A further question still to be answered is whether aminopropionitrile acts specifically on the phosphatase and whether this enzyme disappears or not, because it is one of many constituents which degrade as the mesodermal cells die. If there were any appreciable inhibitions of calcium-activated enzymes under these experimental conditions, one would expect a more general toxicity which would involve the ectoderm. However, the ectoderm was spared, so that inhibition of calcium-activated enzymes does not appear to be the case in lathyrism.

From all these observations, one cannot escape the fact that the mysterious alteration in tissue metabolism is due to some perversion in the ground substance or matrix of the cartilage in the lesions caused by lathyrism.

It is premature to apply the results of the foregoing investigations to human diseases. The basic mechanism of lathyrism may be similar, but this is not yet proved to be true.

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Diet Therapy

Food Patterns of the Southwest

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IN THIS day of rapid transportation, television and radio communication, widely separated groups of people know and use foods and dishes previously considered typical of certain regional groups. Thus, there cease to be "typical" diets except for those in more isolated areas with limited shopping facilities.

The earliest settlements in the Southwest were made by colonists from Spain and Mexico. They found the nomadic tribes of Indians getting their food supply from wild plants and animals. In addition the more settled groups cultivated fields in which they grew corn, beans, squash, pumpkins, and peppers. As the settlers and the Indians mingled each acquired some of the others' eating habits. The development of ranching, agriculture, and the natural resources (such as potash, gas, oil, and uranium) has brought into the state people with different nationality and regional food patterns. Contacts between these different groups introduced new foods but, as is true in all cultural groups, certain foods and recipes typical in the diet of parents and grandparents continue to be used, some daily and some on holidays and special occasions.

Due to limited employment opportunities in the state for low income groups many Indians and Spanish Americans move into other areas for seasonal employment. When these people come to the physician for medical treatment which includes modification of the diet it is important to interpret in terms of their food patterns. The purpose of this paper is to discuss the typical foods and their preparation, the adequacy of the diet and to show how it may be modified to meet the principles of certain therapeutic diets, yet retain as many as possible of the foods desired by this group of people.

TYPICAL FOODS AND THEIR PREPARATION

Foods which have been used for generations and, therefore, may be considered typical of the Southwest are tortillas, tamales, pinto beans, chile, and certain forms of corn.

Breads: The *tortilla* is probably the bread of choice. It was formerly made from mature corn which was treated with wood ashes (later with lime) to remove the outer husk and then worked into a dough. This dough was shaped into a very thin, round cake which was baked on hot stones or a hot stove lid. Today, most tortillas are made from wheat flour with a small amount of baking powder added. The corn tortilla is still used on holidays and may be purchased in many stores in the Southwest. In the home the size and thickness of the tortilla varies just as the size of rolls or biscuits do. Stores sell a very thin tortilla which may be either 6 or 9 inches in diameter. The tortilla may be served as a bread, to scoop up the beans and juice or it may be used in various dishes, as *enchilada, taco,* etc. For the enchilada the tortilla is heated in a small amount of fat. Then it may be filled with grated cheese, onion, and shredded lettuce and rolled. Or several tortillas may be stacked, like pancakes, with the cheese, onion and lettuce between them. In either method a sauce made of chile is served over them. For the taco the tortilla is heated in fat, folded in the center and filled with shredded lettuce and ground meat sea-

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soned with onion, garlic, and oregano and served with a chile sauce.

To prepare *tamales* lard is added to the lime treated corn or *masa* which is spread on corn husks which have been washed and soaked in warm water. Ground meat seasoned with garlic, chile, and tomatoes or meat stock is placed in the center. The sides of the corn-husks are folded over and tied. These are steamed or cooked in a pressure cooker. A chile sauce may be served over these.

Another bread stuff is the *sopaipilla* which is similar to a biscuit dough but rolled thin and fried in hot, deep fat so it puffs up.

Yeast breads are replacing the tortilla to a significant extent.

Cereals: Oatmeal is the most commonly used breakfast cereal but is rapidly being replaced by the ready-to-eat cereals. *Atole*, a cornmeal gruel served with hot milk, is often used for ill people and women in the postpartum period. Rice, usually cooked in milk, is served as a dessert. Spaghetti, macaroni, etc., are used frequently, especially when potatoes are expensive.

Dried beans, either pinto or calico beans, may be eaten several times a day by some Spanish-American families but only one to three times a week by others. Little or no fat may be used in the original cooking but they may be reheated by pan-frying, usually in lard. They may be reheated a second time by frying, "re-fried beans." The beans cooked without fat, when strained or puréed, have proved to be very satisfactory for feeding three-to-four-month-old infants when eggs and meat are not available. It has been a custom of long standing among the Spanish-Americans to feed the juice from the cooked beans to babies but the juice plus the pulp is more nourishing.

Meat, Fish, Poultry and Game: These are well-liked foods which are used frequently when the income permits. The Indians who own flocks of sheep and goats eat meat several times a day when they butcher an animal. How often they butcher depends upon the size of their flock. The picture would be the same during the hunting season. When the Indians and Spanish-Americans must buy these foods they are used only two to three times a week.

Dairy Foods: Eggs may be eaten daily if the income permits but the average intake is two to three times a week. They are usually served fried for breakfast.

Milk was a basic food in the diet when this was a more rural area and people had their own cows or goats. When purchased it seems like an expensive food so little is used except for the baby. Evaporated milk is used for infant feeding, on cereal and in cooking. It may be used for drinking but fresh milk is generally preferred. Very little milk is used in cooking. Cheese made from goat's milk is a popular ingredient of many recipes. However, it is often difficult to get people to use any quantity of the cheddar or American cheese commonly available in the stores.

Vegetables and Fruits: Chile is a common ingredient of many southwestern recipes. The chile, a hot pepper, may be used in either the green or ripened stage. The most commonly used form is the ripened, which is dried and then ground into a powder as used. The canned or frozen green or red chile is also used. The chile sauce served on enchiladas, tacos, etc., may be made with cooked red chile or the chile powder. Tomatoes may be added and it may or may not be thickened with flour. Other seasoning, such as onion, garlic, or oregano, may be used. Green or red chile or the powder is added to many foods such as beans, meat, and potatoes.

Corn is a popular vegetable which may be served as *posole*, which is similar to hominy, or *chicos* which is green corn steamed and dried on the cob. Fresh and canned corn is popular.

Tomatoes and lettuce are the most commonly used vegetables, with string beans, peas, celery, squash, and beets ranging next in popularity. Carrots are being used more frequently. Potatoes were formerly a basic food, used one to three meals, daily. When the price is high and the quality poor their use decreases to every other day or sometimes only once a week. They are usually fried.

Wild greens, such as lamb's quarter (*quelites*), purslane (*verdulagas*) were formerly used both fresh and canned or dried for winter use. They are still used by the older people in the more isolated areas but the younger ones do not know or use them. Most vegetables are cooked too long.

The frequency with which fruits are used depends upon their availability and price, therefore, their use would range from once daily to once a week. Oranges, apples, bananas, and canned peaches are the most popular. If fruit is grown locally apples, peaches, apricots, plums, and pears may be canned at home.

Fats: Butter, even in small quantities, is preferred to oleomargarine. However, through education the number using the less expensive oleomargarine is increasing. Mutton fat is used by the Indians and lard by the Spanish-Americans but both groups are using more of the hydrogenated fats.

Sweets: Large quantities of sugar, soft drinks, and other sweets are used by both groups. Two or three teaspoons of sugar may be used on a serving of cereal. Typical desserts from the "old" days are not as high in sugar. For example, the *biscochito* is similar to a sugar cookie but not as sweet. For the *empanada* a dough similar to the sopaipilla is used. This is filled with a nut and fruit mixture or a nut and meat mixture similar to mincemeat, then fried in deep fat. Sweet rolls purchased at the store are popular, especially for breakfast.

Seasonings: The ground red chile, onions, and garlic are the most commonly used seasonings. Oregano, coriander seeds or leaves, dried mint, parsley, lemon juice, nutmeg, cinnamon, and saffron are also used by the Spanish-American group. Formerly, many wild herbs were dried for seasoning but this practice is decreasing. All groups in the Southwest use large quantities of salt and many use black pepper quite freely.

A high percentage of the people drink large amounts of coffee and in many families the young children are given coffee.

PROBLEMS OF DIETARY ADEQUACY

The dietary deficiencies usually encountered in the Southwest are in protein, calcium, riboflavin, and ascorbic acid. Limited income may be the major factor in some cases but, primarily, the deficiencies are attributable to the failure to appreciate the importance of an adequate diet and a lack of knowledge of the relative value of various foods and what constitutes an adequate diet.

The low intake of dairy foods accounts for the deficiency of calcium and riboflavin and affects the protein intake. The dry skim milk, available at low cost, could be a most valuable addition to the diet. However, it requires an intensive educational program to get the families to use it. Meat and eggs are well liked, so cost is the factor that prevents them from getting sufficient protein from these sources. Dried beans are cooked daily by some families but the cost of fuel and the feeling that beans are not a "good" food may decrease their use to once or twice a week. Education is needed on the value of protein from beans with emphasis on the need to supplement them in the same meal with animal protein, such as a glass of milk.

Frequently, no differentiation is made by the homemaker between the food value of citrus and other fruits. So there is need for education in this field if an adequate intake of ascorbic acid is to be achieved. Fresh, frozen, or canned chile is a good source of vitamin C. It is used liberally by the adults but the children, generally, do not acquire a taste for it until they are ten or eleven years old. If raw cabbage were used in salad instead of lettuce, this would increase the intake of vitamin C. Although potatoes are not rich in this vitamin they supply an appreciable amount if properly cooked and used often. The substitution of rice, spaghetti, etc., for potatoes represents not only a loss of ascorbic acid in the diet but also of iron and thiamine.

Iron deficiency is sometimes observed among women who have had frequent pregnancies and in older infants who receive only milk. Attention needs to be paid to the ascorbic acid and iron contents of the diets for these groups.

A suitable pattern for an adequate diet which would include the foods typical of the area is as listed on the facing page.

Such a pattern is helpful when planning therapeutic diets according to the physician's prescription and adapted to the patient's food preferences. The latter is essential in obtaining the patient's cooperation in eating the diet prescribed.

Foods	*Daily Servings*
Milk, fresh, pasteurized, evaporated, or dry skim	2 cups for adults 3–4 cups for children 4 cups for pregnant women
Meat, fish, or poultry or eggs, cheese or dried beans or peas	2 to 3 servings
Ascorbic acid-rich foods:	1 serving, 2 servings for teenagers or pregnant women
Rich sources: oranges, grapefruit, or their juice	
Good sources: tomatoes, raw cabbage, or green chile	
Vegetables	2–3 servings
Green or yellow vegetables several times a week, daily if dry skim milk is used	
Potatoes—frequently	
Other fruits	1 to 2 servings
Enriched or whole grain bread or cereal or tortillas made with milk and enriched flour	At each meal
Butter or fortified margarine	2 tablespoons
Sweets	Limit as much as possible

SUGGESTIONS FOR PLANNING THERAPEUTIC DIETS

Calculated Diets

Low calorie, diabetic, etc., diets. The exchange lists are readily used in the calculation of these diets.

(1) Nonfat milk solids need to be emphasized when fresh milk is too expensive.

(2) *Vegetable Exchanges:* Chile—fresh, canned, or frozen—is of comparable nutritive value with green pepper and should be included with group A vegetables. Chile powder used for seasoning has negligible food value.

Continual emphasis must be placed on the use of green vegetables for their carotene content, for iron, and for ascorbic acid.

(3) *Fruit Exchanges:* When income is restricted, the amount of fruit which can be used may vary from once a day to once a week. Obviously, the ascorbic acid level of the diet may be jeopardized. It may not be realistic to include two servings of fruit daily. A careful evaluation will then need to be made of the wisest choices of vegetables as well as fruits. For example, tomatoes, greens, and cabbage are reliable sources of vitamin C and may replace in part the usual stated allowance of fruit. Fresh fruits, in season, will provide more adequate levels of ascorbic acid, while many canned fruits such as pears, peaches, apples, cannot be relied upon for the vitamin. In fact, in terms of money spent these canned foods may provide very little nutritive value in comparison with other foods. Sometimes the patient can be shown how to have sufficient money for fruits by restricting the amounts of sweets, fats, and coffee.

(4) *Breads:* The relatively high intake of the filling breadstuffs and beans by people with restricted incomes presents a special problem in the calculation of low calorie and diabetic diets. When the amount of fruit available is restricted, the patient should be instructed that he may occasionally substitute 1 bread exchange for $1^1/_2$ fruit exchanges. However, he must be cautioned not to make such substitution a routine practice.

One store-size tortilla (6 inches in diameter) may be used for one bread exchange. One-half cup posole is also equivalent to one bread exchange.

One-half cup cooked beans provides as much protein as 1 meat exchange and as much carbohydrate as $1^1/_2$ bread exchanges.

(5) *Meat Exchanges:* When the income is limited, an increasing proportion of protein will be provided by beans. When $^1/_2$ cup beans is substituted for one meat exchange, it is necessary to omit $1^1/_2$ bread exchanges and to add 1 fat exchange. In other words, 1 oz meat plus $1^1/_2$ bread exchanges are equivalent to $^1/_2$ cup beans plus 1 fat exchange. When beans are used as a daily item in the diet, it is, no doubt, easier to include them as a separate item rather than confusing the patient with the modification of bread, meat, and fat exchanges.

When the amount of meat is reduced, it is essential that some of the milk be taken at each meal to provide more adequate supplementation of the incomplete protein.

(6) *Fat Exchanges*: Fortified margarine should be emphasized when income is restricted.

Preparation. Since fried foods are especially well liked, the patient must learn to eat foods prepared in other ways. For example, meats

may be broiled, roasted, or stewed; potatoes may be baked, boiled, or mashed (using milk but not fat); beans may be boiled or baked using some fat from the fat exchanges calculated in the diet.

Artificial sweeteners may be indicated for cereals, coffee, etc.

Low-Sodium Diets

(1) Since most people in this area are heavy salt eaters the adjustment to this diet is quite difficult.

(2) Protein. The frequent use of dried beans is an advantage as they are much lower in sodium than the other protein foods. Emphasis must be placed on not using canned or prepared meats as bologna, wieners, corned beef, etc.

(3) Breads. In breads made at home (tortillas, biscuits, yeast bread, etc.) the salt can be omitted without affecting the texture. In quick bread (biscuits, tortillas, pancakes, etc.) low-sodium baking powder should be used. This may be purchased in many stores.

(4) Vegetables. If the income is limited the patient may not be able to afford fresh or frozen vegetables. Those canned without salt are more expensive than the regular canned ones. Celery and beets which are frequently used are high in sodium.

Soft or Bland Diets

To persons accustomed to foods highly seasoned with chile the bland or soft diet is very tasteless and difficult to accept.

(1) Since many foods are fried it will be necessary to suggest other methods of cooking (as mentioned under Low Calorie Diets).

(2) Protein foods present a problem for the patient with a limited income. Dried beans cooked without fat and puréed are tolerated by most patients.

(3) Whole wheat breads are not generally used. Oatmeal is a popular cereal so it will be necessary to teach the patients to strain it.

(4) Fruits and vegetables probably will not be available in adequate amount in the low income diets.

Following are examples of menus based upon the pattern for an adequate diet with the variations that might be made of a low caloric diet, low sodium diet with 800 mg of sodium and a soft or bland diet.

TYPICAL SAMPLE MENUS

LOW CALORIE (1,200 CALORIES)

Breakfast

1/2 cup orange juice
1 egg
1 slice toast or 1 tortilla or 1/2 cup cooked cereal
Coffee
1 cup skimmed milk

Lunch

1 cheese enchilada (1 oz cheese, shredded lettuce, and onion, 1 tortilla (store size) heated in 1 teaspoon fat, chile sauce (no sugar)
1/2 cup green beans; no fat
1/2 cup unsweetened applesauce
1 cup skimmed milk

Dinner

Chile con carne (1/2 cup lean ground beef, 1/2 cup pinto beans, seasoned with chile powder)
1 tortilla (store size)
1/2 cup carrots with 1 teaspoon margarine
Lettuce salad (no dressing)
1/2 canned peach (no syrup)
Coffee (no sugar)

SOFT OR BLAND DIET

Breakfast

1/2 cup orange juice
1/2 cup oatmeal, strained
1 cup milk, sugar
1 egg
1 slice toast or 1 tortilla
2 teaspoons margarine
Coffee, cream, sugar

Lunch

Toasted cheese sandwich
1/2 cup green beans
1 teaspoon margarine
1/2 cup applesauce
1 cup milk

Dinner

1/2 cup ground beef
1/2 cup strained pinto beans
1 tortilla with 1 teaspoon margarine
1 cup carrots, cooked
1 teaspoon margarine
1/2 cup vanilla ice cream
Coffee, cream, sugar

ADEQUATE DIET

Breakfast

1/2 cup orange juice
1/2 cup oatmeal with 1 cup milk, sugar
1 soft cooked egg

1 slice whole wheat toast or 1 tortilla
2 teaspoons margarine or butter
Coffee with cream and sugar

Lunch

2 cheese enchiladas (2 tortillas, lettuce, onion, 1/4 cup shredded cheese, 1 teaspoon margarine, chile sauce)
1/2 cup green beans with 1 teaspoon margarine
1 cup applesauce
1 cup milk

Dinner

Chili con carne (1/2 cup ground beef, 1 cup pinto beans, seasoned with chile powder)
1 cup carrots with 1 teaspoon margarine
1 tortilla with 1 teaspoon margarine
1/2 cup ice cream
Coffee, cream, sugar

LOW SODIUM (800 MG SODIUM), 1,200 CALORIES

Breakfast

1/2 cup orange juice
1/2 cup oatmeal cooked without salt; no sugar
1 cup milk
1 slice toast, without salt
Coffee; no sugar

Lunch

1 egg, no salt
Lettuce and tomato salad (no dressing)
1/2 cup green beans
1 tortilla, homemade without salt
1 teaspoon oil
1/2 cup unsweetened applesauce
1 cup milk

Dinner

Salt-free chili con carne (1/2 cup lean ground beef, 1/2 cup pinto beans, seasoned with chile powder)
1 tortilla, without salt
1 teaspoon oil
1/2 cup carrots
1/2 canned peach (no syrup)
Coffee (no sugar)

SUMMARY

The foods that may be considered typical of the Southwest are pinto beans, tortillas made from flour, or lime-treated corn, and chile—either fresh, frozen, canned or in the powdered form.

These foods need to be included, when practical, in planning therapeutic diets. The usual dietary deficiencies that must be considered are protein, calcium, riboflavin, and ascorbic acid. Frying is a common method of food preparation so that patients on certain types of diets will need to be instructed in other methods of cooking.

The problem of an adequate diet for normal or therapeutic situations is partly economic but largely a matter of education. Emphasis must be placed on teaching the correct value of the foods now used, the choice of correct food to supplement these and how to make substitutions in therapeutic diets.

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Nutrition News

György Awarded Honorary Degree by Heidelberg

We are pleased to note that Paul György, M.D., Department of Pediatrics, University of Pennsylvania, a member of the Advisory Board of this Journal, has been awarded an honorary doctor of medicine degree by the University of Heidelberg. This rare distinction recognizes Dr. György's significant contribution in the field of nutrition.

Fifth International Congress on Nutrition

The Fifth International Congress on Nutrition, organized by the American Institute of Nutrition and the U.S.A. National Committee for Nutritional Sciences of the National Academy of Sciences, will be held in Washington, D. C., September 1 to 7, 1960, under the auspices of the International Union of Nutritional Sciences.

Dr. C. Glen King, Executive Director of The Nutrition Foundation, New York City, has been named President of the Congress; Dr. Elmer V. McCollum, Professor Emeritus of Biochemistry, Johns Hopkins University, is Honorary President. Dr. Paul György, Professor of Pediatrics, University of Pennsylvania, Philadelphia, is Chairman of the Organizing Committee.

Eminent nutrition scientists from all over the world will participate in the Congress. In addition to papers submitted for the usual scientific sessions, a number of panel discussions and symposia on major problems in the field of nutrition in its broader aspects will be presented.

There will also be scientific and industrial exhibits. Visits to various scientific laboratories and other places of interest will be arranged. A special program for women guests and general entertainment for all registrants are being arranged.

For additional information write to Dr. Milton O. Lee, General Secretary, 9650 Wisconsin Avenue, Washington 14, D. C.

Coming Meetings of Interest

As a service to our readers we present a list of future meetings which may be of interest.

April 1959

AMERICAN ACADEMY OF GENERAL PRACTICE, San Francisco, April 6–9. Mr. Mac F. Cahal, Wolker Blvd. at Brookside, Kansas City 12, Mo., Exec. Secy.

AMERICAN COLLEGE OF PHYSICIANS, Conrad Hilton Hotel, Chicago, April 20–24. Mr. E. R. Loveland, 4200 Pine St., Philadelphia 4, Exec. Secy.

AMERICAN GOITER ASSOCIATION, Chicago, April 30–May 2. Dr. John C. McClintock, 149½ Washington Ave., Albany, N. Y., Secy.

AMERICAN PHYSIOLOGICAL SOCIETY, Atlantic City, N. J., April 12–16. Dr. Ray G. Daggs, 9650 Wisconsin Ave., Washington, D. C., Exec. Secy.

AMERICAN SOCIETY OF BIOLOGICAL CHEMISTS, Atlantic City, N. J., April 13–18. Dr. F. W. Putnam, Univ. of Fla. Medical School, Gainesville, Fla., Secy.

AMERICAN SOCIETY FOR EXPERIMENTAL PATHOLOGY, Atlantic City, N. J., April 13–18. Dr. J. F. A. McManus, Univ. of Ala. Medical Center, Birmingham 3, Ala., Secy.

AMERICAN SOCIETY FOR PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, Atlantic City, N. J., April 13–17. Dr. Harold Hodge, Univ. of Rochester, Rochester 20, N. Y., Secy.

May 1959

AMERICAN FEDERATION FOR CLINICAL RESEARCH, Chalfonte-Haddon Hall, Atlantic City, N. J., May 3. Dr. George E. Schreiner, Georgetown Univ. Hosp., Washington 7, D. C., Secy.

AMERICAN PEDIATRIC SOCIETY, The Inn, Buck Hill Falls, Pa., May 6–8. Dr. A. C. McGuinness, 2800 Quebec St., Washington 8, D. C., Secy.

AMERICAN PSYCHOSOMATIC SOCIETY, Chalfonte-Haddon Hall, Atlantic City, N. J., May 2–3. Dr. Morton F. Reiser, 265 Nassau Rd., Roosevelt, N. Y., Secy.

AMERICAN SOCIETY FOR CLINICAL INVESTIGATION, Haddon Hall, Atlantic City, N. J., May 3–4. Dr. S. J. Farber, 550 1st Ave., New York 16, Secy.

ASSOCIATION OF AMERICAN PHYSICIANS, Haddon Hall, Atlantic City, N. J., May 5–6. Dr. Paul B. Beeson, Yale Univ. School of Medicine, New Haven 11, Conn., Secy.

SOCIETY FOR PEDIATRIC RESEARCH, The Inn, Buck Hill Falls, Pa., May 8–9. Dr. Clark D. West, Children's Hosp., Cincinnati 29, Secy.

June 1959

AMERICAN DIABETES ASSOCIATION, Chalfonte-Haddon Hall, Atlantic City, N. J., June 6–7. Dr. E. Paul Sheriden, 1 East 45th St., New York 17, Secy.

AMERICAN GERIATRICS SOCIETY, Hotel Traymore, Atlantic City, N. J., June 4–5. Dr. Richard J. Kraemer, 2907 Post Rd., Warwick, R. I., Secy.

AMERICAN MEDICAL ASSOCIATION, Traymore Hotel, Atlantic City, N. J., June 8–12. Dr. F. J. L. Blasingame, 535 N. Dearborn St., Chicago 10, Exec. Vice-President.

THE ENDOCRINE SOCIETY, Chalfonte-Haddon Hall, Atlantic City, N. J., June 4–6. Dr. Henry T. Turner, 1200 N. Walker St., Oklahoma City 3, Secy.

August 1959

AMERICAN DIETETIC ASSOCIATION, Statler-Hilton Hotel, Los Angeles, Calif., August 25–27. Ruth M. Yakel, 620 N. Michigan Ave., Chicago 11, Exec. Director.

AMERICAN HOSPITAL ASSOCIATION, Statler Hotel, New York City, August 24–27. Dr. Edwin L. Crosby, 18 E. Division St., Chicago, Director and Secy.

September 1959

AMERICAN COLLEGE OF SURGEONS, The Traymore Hotel, Atlantic City, N. J., September 28–October 2. Dr. Paul R. Hawley, 40 E. Erie St., Chicago 11, Director.

WORLD MEDICAL ASSOCIATION, Montreal, Canada, September 7–12. Dr. Louis H. Bauer, 10 Columbus Circle, New York 19, Secretary-General.

October 1959

AMERICAN PUBLIC HEALTH ASSOCIATION, Convention Hall, Atlantic City, N. J., October 19–23. Dr. Berwyn F. Mattison, 1790 Broadway, New York 19, N. Y., Executive Director.

November 1959

GERONTOLOGICAL SOCIETY, INC., Statler Hotel, Detroit, November 12–14. Mrs. Marjorie Adler, 660 S. Kingshighway, St. Louis 10, Admin. Secy.

Nutrition Education Programs

The National Vitamin Foundation, in active cooperation with the Commissions on Nutrition of the Pennsylvania State Medical Society and the Philadelphia County Medical Society, is developing nutrition education programs for the practicing physicians. It is planned to present at the monthly meetings of the various county medical societies a discussion of the basic and practical aspects of nutrition as they relate to disease. The following programs have been scheduled for early 1959:

Date	*Speaker*	*Subject*	*Society and location*
April 29	NORMAN JOLLIFFE, M.D. (New York City Department of Health)	Obesity and Coronary Disease	Annual Convention, New Jersey State Medical Society (Section of Medicine), Atlantic City
May 1	SEYMOUR H. RINZLER, M.D. (Kips Bay Health Center, New York City Department of Health)	Coronary Artery Disease and Nutrition	Pennsylvania Academy of General Practice, Bedford Springs Hotel, Bedford
May 2	PAUL GYÖRGY, M.D. (University of Pennsylvania, Philadelphia)	Iron-Deficiency Anemia in Infants and Children	Pennsylvania Academy of General Practice, Bedford Springs Hotel, Bedford
May 6	WILLARD A. KREHL, M.D. (Yale University School of Medicine, New Haven)	Nutritional and Metabolic Aspects of Gastrointestinal Disease	Lancaster County Medical Society, Lancaster, Pa.

Reviews of Recent Books

The Guinea Pig in Research: Biology—Nutrition—Physiology, by Mary E. Reid. Human Factors Bureau, Inc. (Publication No. 557). Washington, D. C., 1958, pp. 87, $2.00.

This booklet will be of help to those who use the guinea pig for biologic, physiologic, and nutritional research. The major points of the subject matter are compiled in five chapters. The first chapter deals with the genetics of 14 strains of guinea pigs, and describes their origin, the system by which they were bred, and methods of maintenance. As is true for mice, it is essential to have this information, since results obtained in experiments conducted on animals with known genetic constitution are often more conclusive than those obtained with random populations. The next chapter gives data on litter size, life span, and body and organ weights of males and females. In the third chapter the physiology of digestion and hematologic data are discussed, the latter with particular reference to variations with ages; there are also data on blood pressure values and on motor activity. In the following chapter nutritional requirements are given and the principal changes occurring in deficiency states or in states of overnutrition are briefly summarized. The last chapter mentions some of the fields in which the use of the guinea pig as an experimental tool seems promising. A short bibliography is added. While the first three chapters supply a good deal of valuable information, Chapters 4 and 5 were, apparently intentionally, kept brief. Correspondingly, the bibliography is far from complete. The booklet is recommended to all who wish to work with guinea pigs.

M. SILBERBERG

Deficiency Disease: Functional and Structural Changes in Mammalia Which Result from Endogenous Lack of One or More Essential Nutrients, by Richard H. Follis, Jr. Charles C Thomas, Springfield, Ill., 1958, pp. 577, $14.75.

Dr. Follis' new book is unusual in several respects. First, it is oriented with the newer concept that nutritional disorders include disturbances ascribed to the many conditioning factors which may "produce general or local reductions or deficiencies of essential nutrients." Second, it is a book dealing with clinical and metabolic features of deficiency states but with a strong emphasis on pathologic changes. This, of course, reflects the author's well-known interest in pathology. As a matter of fact, it is a logical outgrowth of Follis' previous book, *The Pathology of Nutritional Disease*, written ten years ago. Third, it is unusually well documented. There is a bibliography of 1,535 items, and readers will welcome the full author and subject index.

Scrutiny of the organization will reveal a certain amount of duplication. This, however, is unavoidable, since specific deficiency states are discussed after the sections on individual nutrients. Thus, thiamine deficiency is described in detail in the vitamin section. But the beriberi syndrome is discussed 100 pages later. Similarly, vitamin B_{12} and pernicious anemia are separated. Yet the information is so concise and the style so fluent that the reader will find the discussions quite complete in themselves.

The casual reader will note that some sections, notably lipids and carbohydrates, are brief in comparison to others, e.g. vitamins. This "imbalance," however, clearly reflects our present knowledge of nutritional disorders. Science does not advance equally on all fronts.

Attention should be called to a particularly valuable chapter on deficiency disease as a research method in biology and medicine. In addition, the author should be commended for including a discussion of such topics as dental caries, kwashiorkor, endemic goiter, celiac disease, and the hypokalemic syndrome. Perhaps in a future revision of the book it may be worth including disorders such as atherosclerosis which may be related to an imbalance or excess of certain nutrients, rather than limit the topics to deficiencies only.

This is a valuable book because of its emphasis on structural and functional changes resulting from the endogenous or exogenous lack of one or more nutrients. It is printed on good paper; the illustrations and type are excellent. It will prove to be a useful addition to nutritional literature.

S. O. W.

Diseases of the Liver and Biliary System, ed. 2, by Sheila Sherlock. Charles C Thomas, Springfield, Ill., 1958, pp. 719, $11.50.

Doctor Sherlock has brought together a combination of summaries of her own original work in liver disease and concise epitomes of the pertinent work of others into a remarkably well-organized, useful, and up-to-date monograph. In her writing, Dr. Sherlock has displayed sound clinical orientation in her field, skill in simplifying data, and excellent judgment in including essentials and excluding trivia. It is remarkable that in 719 pages she has compressed so much useful material in so readable a text.

In addition to covering the clinical aspects of hepatic disease, including pathology, in adequate but surprisingly brief fashion, Dr. Sherlock has provided a stimulating view of the important basic science developments of most recent vintage. Thus the classical descriptions of the morphology of the liver are augmented by data obtained by electron microscopy and histochemistry on the fine structure of the liver cell. The clinical matter presented has an extremely contemporary flavor and includes such subjects as veno-occlusive disease, penicillamine for Wilson's disease, the pathologic physiology of hepatic circulation, and a concise section on the biochemistry of the liver. The text is well illustrated, many of the illustrations from Dr. Sherlock's own clinical material; and its useful index is quite complete. Bibliographic references are adequate but unobtrusive.

The chapter on the relationships of nutrition and liver disease is, however, somewhat disappointingly, though understandably, brief. In the discussion on fatty liver, no mention is made of the fatty liver of diabetic acidosis. The summary of the experimental data on the effects of alcohol on the liver is, however, provocative and apt. The summary on experimental cirrhosis in animals, with emphasis on the clinical implications, is useful for the clinician as well as the experimenter.

The book should prove of special value to the practicing gastroenterologist and to the investigator interested in any aspect of hepatic physiology or liver disease.

J. B. HAMMOND

Nutrition and Atherosclerosis, by Louis N. Katz, Jeremiah Stamler, and Ruth Pick. Lea & Febiger, Philadelphia, 1958, pp. 110, illus. 67, $5.00.

The authors have previously written excellent reviews on experimental atherosclerosis and in this volume have expanded on the Henry Jackson Lecture given by Dr. Katz.

There are four chapters on the relations between diet, blood cholesterol levels, and heart disease, and on the effects of experimental diets on animals and men. This provides a complete survey of this important problem. Chapter 6 discusses the importance of endocrine factors, heredity, physical activity, smoking, and emotional stress in determining the rate of development of atherosclerosis. There is almost no discussion of the effect of these influences on blood coagulation, and on the precipitation of thrombotic accidents. There is a full discussion on the effects of estrogen in inhibiting coronary atherosclerosis in chickens and on the authors' study of effect of estrogens on survival of men with myocardial infarctions. Chapter 7 covers prophylaxis of atherosclerosis in man. There are only two paragraphs on anticoagulants, but an adequate discussion of diet and four pages on estrogens. There is no mention of nicotinic acid, which in the past two years has established itself as the cheapest, most effective, and most harmless agent now available for lowering blood cholesterol.

This book is of great value as an introduction to those unfamiliar with the field and has a very complete bibliography.

WILLIAM DOCK

Thirst: Physiology of the Urge to Drink and Problems of Water Lack, by A. V. Wolf. Charles C Thomas, Springfield, Ill., 1958, pp. 426, illus. 44, $12.50.

This is a most useful work which has brought together much of the useful data on thirst, drinking, and satiety in relation to body fluid and its regulation. The case of drinking sea water receives special treatment. Special problems of thirst are illustrated by actual examples and case histories, including accounts of actual instances of exposure to water deprivation which have an important bearing on the phenomena of thirst from the physiologic standpoint.

Considerations of water balance introduce the problems. The concept of fugacity or "escaping tendency" to include all the factors (including hydrostatic pressure) in fluid translocation is valuable, since it is to be distinguished from osmoticity. The importance of Laplace's law is emphasized as it correlates pressure-tension-radius relations with the osmotic equilibria of cellular and extracellular fluids. These are but two examples of the many fundamental problems considered.

Theories of thirst are extensively treated, and data supporting the various concepts are well documented The presentation of newer control theories is good. It is also pointed out that satiety is a separate entity which can be distinguished from thirst and drinking.

Volume receptors in the regulation of fluid volume are thoroughly considered, and the necessary relation of volume to salt is stressed. Drinking and renal excretion affect fluid volume: The thought is presented here that volume may influence thirst and the kidney.

Thirst, with its multiple problems, is presented from many aspects. As a single example, from many, is the example of sea-water drinking. The material here is extensive and well done. In fact, the entire volume can be well recommended.

M. J. OPPENHEIMER

The Interference Microscope in Biological Research, by A. J. Hale. E. & S. Livingstone, Ltd., Edinburgh, Scotland, 1958 (The Williams & Wilkins Co., Baltimore, exclusive U.S. agents), pp. 114, $5.00.

The progress of chemistry and physics in general is reflected in the application of new and difficult methods in biologic research, and it becomes not only desirable but necessary for the biologist to get acquainted with these methods, particularly since biological research is increasingly focused on metabolic activities of cells and on quantitative determinations of cellular components. In the foreword to this book Professor Garry remarks that only a few biologists might be willing or have the opportunity to go back to school and learn such methods; a simple text as the present one, therefore, serves a most useful purpose.

This book fully informs the novice in the field about the basic facts and the significance of interferometry and the use of the interference microscope for quantita-

tive cytophysical studies. The first two of seven chapters briefly summarize the physical basis of interferometry and describe the types (beam systems) of the interference microscopes. There follows an explanation of the theoretical and practical interpretation of the image patterns and a description and evaluation of the practical methods of measuring optical retardation with a discussion of the cytochemical significance of measurements of this phenomenon. The concluding chapter deals with possible sources of error in the establishment of absolute values of protein, nucleic acids, lipids, carbohydrates, protoplasm, and inorganic constituents. While most of the technical details are left to the experts for analysis, there is much valuable information to the morphologist who is interested in interference as a method for research. The book makes stimulating reading and does not fail to mention pitfalls of the method. To the experimental pathologist, who is aware of the limitations of light microscopy, the book is a welcome guide to a method of approach which promises further progress in the field of histo- and cytochemistry.

M. SILBERBERG

Nutrition for Practical Nurses, ed. 2, by Phillis S. Howe. W. B. Saunders Company, Philadelphia, 1958, pp. 219, $2.75.

This is a practical, simply written booklet that will be an invaluable aid to the practical nurse. It covers a variety of subjects from a concise explanation of nutrition, digestion, absorption, and metabolism to national and religious food habits. The correlation of diet with the many diseases of medical origin is discussed.

DOROTHY SHOGI

BOOKS RECEIVED

Books received for review by THE AMERICAN JOURNAL OF CLINICAL NUTRITION are acknowledged in this column. As far as practicable, those of special interest are selected, as space permits, for a more extensive review.

Ciba Foundation Symposium on Amino Acids and Peptides with Antimetabolic Activity, edited by G. E. W. Wolstenholme and Cecilia M. O'Connor, Little, Brown & Company, Boston, 1958, pp. 286, $8.75.

Congrés International de la Fonction Biliaire: I. Volume des Rapports; II. Volume des Communications Thérapeutique Thermale, Masson & Cie, Paris, 1958, I, pp. 462; II, pp. 172, 5,000 fr.

Long-Term Illness: Management of the Chronically Ill Patient, edited by Michael G. Wohl, W. B. Saunders Company, Philadelphia, 1959, pp. 748, $17.00.

Abstracts of Current Literature

CHARLES R. SHUMAN, M.D., EDITOR

WALTER H. ABELMANN, M.D., *Boston*
MARGARET W. BATES, D.SC., *Pittsburgh*
ELIAS COHEN, PH.D., *Buffalo*
A. B. EISENSTEIN, M.D., *St. Louis*
JAMES B. HAMMOND, M.D., *Indianapolis*
GUY HOLLIFIELD, M.D., *Charlottesville*
M. K. HORWITT, PH.D., *Elgin*
F. E. HYTTEN, M.B., B.S., PH.D., *Aberdeen, Scotland*
S. M. LEVENSON, M.D., *Washington*
JOHN F. MUELLER, M.D., *Cincinnati*
MORTON J. OPPENHEIMER, M.D., *Philadelphia*
THEODORE C. PANOS, M.D., *Little Rock*
FRANK E. RICE, PH.D., *Chicago*
JAMES H. SHAW, PH.D., *Boston*
MARTIN SILBERBERG, M.D., *St. Louis*
JANICE M. SMITH, PH.D., *Urbana*
W. H. J. SUMMERSKILL, D.M., *London*
GEOFFREY WALKER, M.B., *Oakland*
JOHN WATERLOW, M.D., *Kingston, Jamaica*

MALNUTRITION

Several types of heart disease have been described in association with protein malnutrition. The morphologic changes in the heart and the clinical manifestations vary depending upon the duration and specific deficiency involved. In the case of thiamine deficiency the actual pathogenesis of cardiovascular disorders arising in these patients is controversial. It has been shown by Bing that the myocardium can utilize lactate or fatty acids as efficiently as carbohydrate for energy production so that the deleterious effect of hypothiaminosis may be extracardiac rather than primarily cardiac.

Acute Reversible Heart Failure in Africans. H. Grusin. *Circulation* 16: 27, 1957.

Sixteen native African patients (Bantu) with cardiac enlargement and reversible acute heart failure of obscure etiology were studied. All had subsisted on an inadequate diet, low in animal protein and fat, and most were chronic alcoholics. They were maintained for 5 to 10 days on a diet low in thiamine (less than 0.3 mg/day), but otherwise adequate.

On this regimen, without treatment other than bed rest, three of 16 patients responded completely. Six patients did not respond until thiamine was administered, whereupon they compensated within 5 to 9 days, and their hearts returned to normal size within three weeks. Four patients responded partially on the low-thiamine diet and showed full recovery after administration of thiamine. Three patients did not show early improvement on either of the above regimens, two improving only gradually, and one only after digitalis and mersalyl.

Of the 10 patients who responded to thiamine, as well as all 3 patients responding to low-thiamine diet, 9 had clinical signs of high output failure, unlike the 3 patients who did not respond to either diet or thiamine.

An additional group of 10 cases of edema without cardiac enlargement was studied similarly: 8 cases, 6 of which were alcoholics, responded on the low-thiamine diet and bed rest, and these included 4 patients with signs of high output failure. Two patients did not improve until given thiamine.

In the author's opinion the amount of thiamine in the "low thiamine" diet was too low to be therapeutic. The author believes that the patients who responded to this diet represent a syndrome of hypervolemia with nutritional edema not related to thiamine deficiency.

W. H. ABELMANN

Liver Enzymes in Human Undernutrition. K. L. Mukherjee and N. K. Sarkar. *Brit. J. Nutrition* 12: 1, 1958.

The nitrogen, iron, and enzyme content of liver biopsy material was studied soon after admission to the hospital and shortly before discharge in 12 adult patients with nutritional edema and seven infants with kwashiorkor. Total liver nitrogen was low initially, but became normal after treatment. The iron content and catalase activity appeared to be related to each other, both being abnormally high at first but falling to normal after clinical recovery. There was on the average a 70 per cent reduction in cholinesterase activity at the height of malnutrition, and the alkaline phosphatase content was very high, the latter perhaps reflecting the relatively high dietary carbohydrate content. Both reverted to normal after treatment. W. H. J. SUMMERSKILL

Previous work has been reported which indicates that patients with glomerulonephritis receiving a normal pro-

tein and caloric intake have fewer sequelae of the disease during a two-year follow-up than those treated by the method described below.

Influence of Fasting on the Immunological Reactions and Course of Acute Glomerulonephritis. J. Brod, L. Pávková, V. Fencl, Z. Hejl, and E. Kratková. *Lancet* 1: 760, 1958.

Fasting has been considered good treatment for acute nephritis for many years, but many physicians have abandoned it because it seemed to have no rational basis. In this investigation, the effect of fasting on acute nephritis is examined, particularly in relation to the level of "collodion agglutinins," which are held by some to be the antikidney antibodies produced by an autoallergic reaction.

Two groups were compared. In one the disease was treated by bed rest and light diet, the other was given only 100 ml of fruit juice daily for 60 hours followed by a 500-calorie diet consisting mainly of fruit and vegetables. In the fasting group, the agglutinin titer, blood pressure, and glomerular filtration rate all returned to normal significantly sooner than in the others.

The authors state: "We believe that fasting reduces the severity of the antigen-antibody reaction responsible for acute glomerulonephritis and should be an essential part of treatment." F. E. HYTTEN

The following report agrees with my personal experience (C. R. S.) with the use of rauwolfia preparations. There is an occasional patient exhibiting significant weight gain during therapy with these agents.

Use of Derivatives of Rauwolfia Serpentina in the Treatment of Malnutrition. L. G. Dinkin. *New York J. Med.* 58: 505, 1958.

It had been noted that patients with hypertension treated with rauwolfia preparations often showed an increase in appetite and body weight. This study was based on 42 patients observed in a nutrition clinic. Included in this group were five with neoplasm, two with heart disease, and others with asthma, ulcer, epilepsy, etc. After a control period, during which diets and vitamin therapy (and in some instances antibiotics and testosterone) were used, the patients were placed on either whole root of *Rauwolfia serpentina* or the alkaloid reserpine. After a treatment period ranging from 4 to 24 weeks the drug was discontinued, and "usually" a placebo was substituted for 8 to 10 weeks. Administration of the drug was then resumed.

Of 42 patients so treated, 35 gained weight during the period of treatment. During the average treatment period (15 weeks), the total weight gained ranged from 2.5 to 20 pounds for an average of 6.6 pounds. The weekly gain in weight, therefore, was 0.44 pounds. Seven patients did not gain weight, and four of these lost weight during the 6-to-12-week treatment period. Very few side effects were said to be observed, and after discontinuation of rauwolfia therapy there was usually an arrest of the weight gain or a loss of weight. The author states that most of the patients treated with rauwolfia derived some permanent benefits from this form of therapy. S. O. WAIFE

It is difficult to measure accurately total body water in edematous states owing to compartmentalization of the extravascular and, perhaps, vascular fluids. It is questionable whether the urea method will improve this situation.

Validity of the Urea Method for Estimating Total Body-Water in Malnutrition. S. G. Srikantia and C. Gopalan. *Lancet* 2: 1037, 1957.

In 5 normal adult subjects and 5 adults with nutritional edema due to severe protein deficiency, total body water was estimated by the urea and the antipyrine methods.

The urea method gave from 94.4 per cent to 104 per cent of the estimate given by antipyrine in the normal subjects and from 95.3 to 104.4 per cent in the edematous subjects; the mean was about 101 per cent in both groups. It is concluded that the urea method is suitable for the estimation of total body water "even in malnourished patients," but this overlooks the well-known fact that antipyrine itself is unsatisfactory in edematous states. F. E. HYTTEN

Effect of Fasting on Muscle Proteins and Fat in Young Rats of Different Ages. S. N. Hagan and R. O. Scow. *Am. J. Physiol.* 188: 91, 1957.

Rats 30 to 70 days of age were fasted for three or more days and changes in the amounts of various protein fractions and fat were measured in the thigh muscle. Only two protein fractions in the muscle, myosin and water-soluble (sarcoplasmic) proteins, were decreased; the stroma and nonprotein nitrogen fractions were unchanged. It was found that only 20 to 27 per cent of the calories that came from the thigh muscle were derived from protein, and the rest were derived from fat. These findings are in agreement with many other reports that during fasting body proteins contribute only a small proportion of the calories that are needed for survival. There was no evidence of edema or "water-logging" in the muscle of these fasting animals.

AUTHORS

INTRAVENOUS FAT ALIMENTATION

There are many difficulties encountered by investigators in this field. The stability of the fat emulsions under study appears to be satisfactory. Despite improvement in these preparations from the standpoint of toxic effects, thermogenic responses continue to occur in a significant number of recipients. Febrile reactions in the absence of a rise in serum bilirubin indicates that factors other than hemolysis must be sought as a cause of toxicity.

Tolerance of Infants and Children to Fat Administered Intravenously. L. Williams and R. Kay. *Pediatrics* 20: 809, 1957.

Data from 146 infusions administered to 78 subjects

are presented. Age range was from 10 days to 13 years, with 19 infants less than three months of age and 15 between three months and one year. The preparations used were 15 per cent emulsions of fat providing 1,518 calories per liter. Olive oil emulsions were used in 50 infusions and cottonseed oil emulsions in 96. The preparations contained 4.2 g of glucose/100 ml and were stabilized with soy bean phosphatidein and a synthetic emulsifying agent, Pluronic F68. Infusions were administered for an average period of six hours at rates between 3 and 7 ml/kg/hr with a total volume not exceeding 500 ml daily. Eighteen subjects were given successive daily infusions for three to six days. In 15 of these there were no significant changes in concentration of NPN, bilirubin, or alkaline phosphatase; the cephalin flocculation test, concentration of urobilinogen in the urine, and routine urinalysis were not abnormal. Three instances of increased values in the zinc turbidity test were noted. Four infants developed mild anemia.

During infusions administered at an average rate of 5 ml/kg/hr for periods of four to six hours, concentrations of ketones in the blood increased an average of 7.1 mg/100 ml (1.2 mM/l) in nonfasted subjects and 13.2 mg/100 ml (2.3 mM/l) in fasted subjects. This is interpreted as suggestive evidence of the utilization of fat during the infusion. Temperature elevations of more than 1.1°C (2°F) occurred during or after the infusion in 23.0 per cent of infusions with a marked increase in frequency at infusion rates greater than 5 ml/kg/hr. Vomiting occurred in 12.3 per cent. An addendum indicated that an additional 106 infusions had been completed with a more highly refined preparation and that the instance of fever in this group was reduced to 16.9 per cent, with no immediate reactions of dyspnea, flushing, or nausea as were seen in the original series. The incidence of vomiting during infusion was unchanged.

T. C. PANOS

Experiences in Human Beings with an Improved Fat Emulsion for Intravenous Administration. J. F. Mueller. *J. Lab. & Clin. Med.* 50: 257, 1957.

The author reports on the clinical experience with the use of an improved fat emulsion for intravenous administration in 151 subjects, comparing these results to prior results with an emulsion of similar composition in 110 subjects. The emulsions differed only in the purification of the soybean phosphatide emulsifier.

The reaction rate was 51 per cent with the old and 33 per cent with the new emulsion. Fever accounted for 88 per cent of the reactions with the new emulsion. There was no severe reaction with the new preparation. No attempt was made to assess the beneficial effects of the new or old emulsion.

The author believes that the new preparation is a practical and usable material. The main difficulty is the febrile reaction and the instability of the preparation when mixed with electrolyte or amino acid solutions.

K. R. CRISPELL

In addition to an adequate supply of energy provided by intravenous fat emulsions, a source of nitrogen is required to prevent nitrogen depletion in postoperative patients. The reversal of nitrogen losses by augmentation of caloric intake indicates that these losses are the result of poor nutritional intake during the postoperative period.

Metabolic Alterations in Surgical Patients: IX. The Influence of Intravenously Administered Fat Emulsions on Nitrogen Balance in Postoperative Patients. S. Levey, H. Krieger, J. W. Benson, J. H. Davis, and W. E. Abbott. *J. Lab. & Clin. Med.* 49: 61, 1957.

The effect of administering fat emulsions intravenously to surgical patients who were being maintained on protein hydrolysates and hexose solutions was studied. Two patients with carcinoma of the esophagus were maintained on this regimen, one showing positive nitrogen balance and one "less negative" nitrogen balance. Four patients undergoing subtotal gastrectomy were maintained on the intravenously administered protein hydrolysates, hexoses, and fat emulsions. A five-day nitrogen balance period is presented (one day pre- and four days postoperative). This regimen produced a cumulative nitrogen deficit of 3 to 14 g as compared to 30 to 35 g. The latter figures were from previously published data in a study where only protein hydrolysates and hexose were given intravenously. The effect of the fat was thought to be due to caloric increase and not to a specific nitrogen-sparing effect of fat.

"The large nitrogen deficits following surgical trauma of the soft tissue thus seem to be mainly the result of poor postoperative nutrition rather than due to the stress reaction." This may be true, but the authors have not presented adequate data to justify this statement. The postoperative nitrogen balance depends to a great extent on the previous nutritional state of the patient. The studies of patients presented here were of patients who might not have been expected to show a marked degree of postoperative negative nitrogen balance. The results are suggestive but not definitive in proving that the negative nitrogen balance following surgery is nutritional.

K. R. CRISPELL

The Use of a Fat Emulsion as a Source of Calories in Patients Requiring Intravenous Alimentation. H. Krieger, W. E. Abbott, S. Levey, and W. D. Holden. *Gastroenterology* 33: 807, 1957.

The authors describe the effects of a 15 per cent fat emulsion (Lipomul) in dogs and humans. Intravenous fat substituted for the fat content of the diet for a four-day period caused no change in the positive nitrogen balance of the dogs following the substitution. A series of 300 postoperative surgical patients were given the fat emulsion, usually 600 ml per day for the first three to four days after surgery, with no significant reactions. In a group of 10 patients undergoing subtotal gastrectomy for peptic ulcer, receiving only glucose solutions parenterally, the average cumulative nitrogen deficit for five days postoperatively was 57.9 g. In a similar

group receiving protein hydrolysates, the cumulative five-day nitrogen deficit was reduced to 38.2 g. In contrast to the first two groups, a third group received intravenous fat emulsion as well as protein hydrolysates and glucose. These patients had a five-day cumulative nitrogen deficit of only 7.3 g, indicating that their protein and calorie needs were almost entirely met by parenteral alimentation alone. The authors emphasize the need for protein hydrolysate as well as adequate calories to achieve a positive nitrogen balance. Additional data are needed on patients receiving intravenous fat emulsion for longer periods, including information on the fate of the intravenously administered fat.

J. B. HAMMOND

Effects of Intravenous Administration of Fat Emulsions and Their Emulsifying Agents. I. Effects on Clearing Factor Activity, Electrophoretic Pattern and Clotting Time of Blood of Dogs. W. F. Lever and B. Baskys. **II. Effects of Phosphatide Preparations on the Coagulation of the Blood of Dogs.** E. Klein, J. V. Garrett, and W. F. Lever. *J. Invest. Dermat.* 28: 317, 321, 1957.

Very preliminary data in dogs are offered to suggest that the infusion of the soybean phosphatide utilized as an emulsifying agent in fat emulsions is associated with an increase in "clearing factor activity" in the plasma, increase in electrophoretic mobility of the lipoproteins, and decreased coagulability of the blood. The latter is purportedly due to the presence of an anticoagulant supposedly associated with the "clearing factor activity," probably heparin, since the above effects can be abolished with protamine.

Although the amount of phosphatide necessary to produce the coagulation changes is not made clear, these findings are not consistent with those of others including the abstracter, who has found increased coagulability of the blood following single infusions of fat emulsion in humans as well as in animals. Likewise, with a much more sensitive test for "clearing factor activity" very little such enzyme could be demonstrated in the blood of humans following fat infusion. Species differences may play a role. More complete data from this laboratory will be awaited with interest.

J. F. MUELLER

MILK

Differences between cow's milk and human milk with respect to amino acid composition have revived the perennial discussions concerning the possible superiority of one over the other in human nutrition. It is important to realize that the lysine content of milk is sufficient to supplement the possible deficiencies in this amino acid found in cereal proteins.

Formulas Made from Cow's Milk Provide Infants' Needs for Proteins and Amino Acids. F. E. Rice. *J. Dairy Sc.* 40: 1632, 1957.

Human milk averages 1.2 g protein/100 ml. Of the total calories in human milk, protein contributes 9 per cent or less. A baby receives generally from 2 to 2.5 g protein/kg body weight per day, and in many cases less than 2. Cow's milk averages 3.3 g protein/100 ml; and the usual infant formula prepared from cow's milk (with added carbohydrate) contains 2.3 g/100 ml, representing more than 15 per cent of the caloric content of the formula. On such a formula the baby receives about 3.7 g protein/kg per day. From calculations such as these, and from observations on infants and animals fed at levels of protein represented by average human milk on the one hand and a typical formula on the other, some nutritionists have suggested that breast-fed babies may receive no more than marginal amounts of protein, particularly from mothers who are producing milk of less than average protein content.

The author has tabulated infant requirements for the various essential amino acids as reported in the current literature, together with calculations of the amounts of these amino acids provided by 2.5 g human milk protein and 3.7 g cow's milk protein, such as the baby would receive from (high) average human milk and from the usual formula. Again the comparisons reveal that with respect to most amino acids the formula better provides the baby with its apparent needs than does human milk.

The analyses show that lysine intake from a cow's milk formula is well above the infant's requirement for this amino acid and is much greater than that supplied by human milk.

The use of evaporated milk as the form of cow's milk in the feeding formula, which has been commonly practiced in the past 25 years, has effectively solved the curd problem. In a number of laboratories it has been demonstrated that there is no loss in biologic value of the protein from processing raw cow's milk into evaporated milk. The amino acid patterns of cow's-milk and human-milk proteins are essentially alike and follow closely the pattern of amino acid requirements of the infant.

The question of whether the usual milk formula may provide an intake of protein higher than necessary, and one that might tend to overload the infant's excretory capacity, is clearly answered in the negative.

AUTHOR

The Nutritive Value of Milk Proteins. K. M. Henry. *Dairy Sci. Abstr.* 19: 603 (Part I) and 691 (Part II), 1957.

This is an excellent review of the literature, mainly of papers published since 1945; 182 references are cited. Values reported from various laboratories of amino acid content of the individual proteins of milk, as well the total protein composite, are tabulated.

The protein entity is nearly "ideal" in amino acid balance. Two international agencies, FAO and WHO, have adopted cow's-milk proteins as a standard for establishing human dietary protein requirements. The milk protein composite contains a little less of the sulfur

amino acid fraction, methionine, and cystine, than does egg protein. However, fur-bearing animals are more sensitive to a lower level of the sulfur-containing amino acids than is man. The author expresses surprise that the adequacy of milk protein as a carrier of lysine is ever questioned. It is richer in lysine than is egg protein. In that respect she considers it a particularly valuable supplement in diets containing mainly cereals. There is generally good agreement between laboratories reporting on digestibility and biologic value of milk protein. Variations appear to be due to different analytical methods and to the quality of the samples used.

Attention is called to the differences in casein and lactalbumin in amino acid content and in the effectiveness of these proteins in supporting growth of normal animals, and in regeneration of the proteins of plasma and liver in protein-depleted animals. The therapeutic value of milk protein is discussed in relation to kwashiorkor and other conditions caused by dietary inadequacies.

The author makes a careful review of the literature on the effects of heat treatment and of storage on dairy products, particularly dry milk and evaporated milk. She concludes: "Carefully controlled heat treatment and good storage conditions cause no loss in the nutritive value of milk proteins. Damage may be caused by prolonged heating at high temperatures or by storage under conditions with access to air or moisture."

F. E. RICE

Nutritive Value of the Proteins of Stored Instant Nonfat Dry Milk. A. Z. Hodson and C. B. Miller. *Food Technol.* 11: 89, 1957.

The newer nonfat dry milks are usually given low-heat treatments in manufacture; they are packed in glass, laminated foil, or other containers more or less impervious to moisture. Changes that may take place in the storage of such powders have not been determined. Pasteurized market milk as well as freshly manufactured dry milk were used as controls. Protein evaluation was determined by the rat growth method. This was supplemented by lysine assays, as an indication of possible amino acid loss. There was no significant change in protein efficiency or in lysine content after storage even up to two years. F. E. RICE

Further Studies of the Effect of Processing on Some Vitamins of the B Complex in Milk. H. R. Chapman, J. E. Ford, S. K. Kon, S. Y. Thompson, and S. J. Rowland. *J. Dairy Res.* 24: 191, 1957.

Cow's milk, suitably modified, has been used for many years with success in infant feeding. It is richer than human milk in vitamin B_6, B_{12}, biotin, and pantothenic acid. The levels of riboflavin and nicotinic acid are somewhat lower in a cow's milk formula but are believed to provide adequately for the needs of the human infant. The nutritional implications of heat sterilization of milk on these vitamins are of special importance.

From a single bulk of raw whole milk there were prepared, in pilot plants, roller- and spray-dried milk, sweetened condensed milk, and unsweetened "evaporated" milk under conditions designed to parallel those observed in commercial practice.

In addition, samples of the same whole milk were sterilized by a high-temperature (135°C), short-time (2 sec) process (HTST). And other samples were sterilized, "in bottle," at lower temperatures for longer periods of time. In none of these samples was there found a significant loss in riboflavin, pantothenic acid, nicotinic acid, vitamin B_6, or biotin. In all samples except HTST sterilized milk, thiamin was destroyed in amounts ranging from less than 10 per cent to 40–50 per cent, the loss increasing with the severity of the heat treatment. Prolonged high temperature, as applied in the sterilization of "evaporated milk" and "in-bottle" whole milk, caused nearly complete loss of vitamin B_{12}. HTST sterilization resulted in less than 10 per cent loss of either thiamin or B_{12}.

Three brands of evaporated milk and two of sweetened condensed milk were purchased at local food stores, and examined for vitamin B_{12}. Evaporated milk samples varied from 1.0 to 1.9 μg/g, sweetened condensed 3.0 to 6.3. Samples of "National" dry milk, supplied by the Medical Officers of Health, were found to contain 13 to 18 μg B_{12} per g. For comparison, the authors give as a "conjectural value" for B_{12} in fresh milk—4 μg/ml.

(*Abstracter's Note:* It has been demonstrated in many studies that pilot-plant operations generally cause more marked changes in foods than when apparently the same conditions are applied in commercial processing.)

F. E. RICE

The Content and Loss of Vitamins in Powdered Milk. R. B. Davydov. *Voprosy Pitaniya* 16: 35, 1957.

The results of an investigation into the vitamin content of milk during the process of evaporation and during storage and also during all seasons of the year are reported.

Content of vitamins A, E, B_1, and B_2 was determined. The content of vitamin A averaged 1.96 mg/kg of dried milk with a variation from 1.12 mg to 2.64 mg. As a result of evaporation 10 per cent of the vitamin A was lost, and after a two-year storage, 40 per cent. The highest content of the vitamin A was in the summer months.

The average content of vitamin E was 5.4 mg/kg of dry milk, with a variation from 4.2 mg to 6.4 mg. During evaporation 22 per cent was lost, and after a two-year storage, 20 to 22 per cent. There were no seasonal variations in the content of vitamin E.

The average content of thiamine was 2.7 mg/kg with fluctuation from 1.8 mg to 4 mg. No substantial changes were noted during the process of evaporation and storage. The highest content of vitamin B_1 was observed in autumn and winter months.

The content of riboflavin averaged 17.88 mg/kg of dry milk, with fluctuations from 9.4 mg to 26.2 mg.

During evaporation 17 per cent was lost, and after a two-year storage, 35 to 37 per cent. The content of riboflavin was higher in milk obtained in summer months than in winter. AUTHOR

Milk Drinking by College Students. L. Mirone and E. L. Whitehead. *J. Am. Dietet. A.* 33: 1266, 1957.

About 9 per cent of college students claim that they do not drink milk. Observation of many thousands of trays in the college cafeteria revealed that 28 per cent of the women's trays contained milk compared to 36 per cent of the men's. At breakfast, 60 per cent of the students' trays contained coffee; 39 per cent, milk. At lunch and dinner, about two-thirds of the trays contained iced tea and about 29 per cent, milk.

S. O. WAIFE

The frequency of allergic symptoms due to penicillin sensitivity adds to the interest of the following report.

Dermatitis Caused by Penicillin in Milk. H. R. Vickers, L. Bagratuni, and S. Alexander. *Lancet* 1: 351, 1958.

Two cases are presented of dermatitis due to sensitivity to penicillin present in milk. The drug had been used to treat mastitis in the cows and in one sample of milk contained 4 units per ml. It is suggested that the American ruling prohibiting the sale of milk from cattle for 72 hours after penicillin treatment should be adopted in Britain. F. E. HYTTEN

The problem of insecticide residues and other toxic factors introduced into cow's milk for human consumption is of great importance and requires continuous surveillance.

Pesticide Residues in Milk. F. A. Vorhes. *J. Agr. Food Chem.* 5: 906, 1957.

The subject of pesticide residues in milk is more serious than in any other food. In dairy foods neither commercial processing nor culinary practice is likely to eliminate the residue. More milk and dairy products are consumed per capita than any other class of foods; and consumption is greatest with the young, the weak, and the sick. Residue tolerances, determined as they usually are, using well-cared-for laboratory animals, cannot be applied in this situation, so that a regulatory agency cannot fairly set maximum permittable tolerances for milk. A further complication in dealing with pesticide contamination in milk is the possibility that in the animal digestive and metabolic system a substance may be formed not identical with the original pesticide which the analytic method is designed to measure, and which might be multiplied in toxicity on its way to being secreted in the milk.

The bovine rumen provides an active environment for chemical change; it would be wise for the dairy industry to select pesticides that could be demonstrated to be inactivated at that point. F. E. RICE

Determination of Small Quantities of 2, 3, 4, 5-Bis (Δ-2-butenylene) tetrahydrofurfural (Repellent R-11) in Milk. P. E. Toren, L. D. Goodhue, W. R. Kirkham, and D. E. Howell. *J. Agr. Food Chem.* 5: 749, 1957.

R-11 has been found to be an effective insect repellent. A method for determining R-11 in milk is demonstrated with a sensitivity of 0.1 ppm. Two independent laboratories participated in this study. Five Holstein cows were sprayed at various intervals with various exposures to repellent up to 20 times that needed for effective fly control. The milk and the butter churned from the milk were tested for R-11 and for two of the most likely metabolites. None of the substances tested for was found to be increased over the controls. A study of the distribution of R-11 between butterfat and skimmed milk following direct addition to milk showed that 82 per cent of chemical was concentrated in the fat phase.

F. E. RICE

Silicon in Cow's Milk. J. G. Archibald and H. Fenner. *J. Dairy. Sc.* 40: 703, 1957.

This is the eighth in a series on the mineral elements of cow's milk. The study was conducted with six cows representing three breeds in the early stages of lactation and barn-fed throughout. Matched pairs of animals were fed with and without added sodium silicate at the rate of 1 g daily (230 mg elemental silicon). Milk from cows on the control diet averaged 1.43 mg silicon per liter. The average for those receiving the supplement was 1.39 mg per liter. There were wide variations between individuals and in the same animal from month to month. While there was no consistent increase in the silicon content of milk as a result of supplementing the diet with silicon, there was observed a definite and significant decrease in the values as the season and the stage of lactation progressed. It was concluded that silicon is a natural constituent of milk, though it is questionable whether it can be classed as an essential dietary element. F. E. RICE

KWASHIORKOR

In malnourished and marasmic children severe pancreatic lesions have been observed at autopsy. Fatty infiltration and reduced nitrogen content of the liver associated with reduced serum albumin and edema are frequently observed. Impaired function of these organs leads to a vicious cycle which limits further the absorption and utilization of essential dietary factors.

Pancreatic Activity in Normal and Malnourished Egyptian Infants. M. K. Badr El-Din and M. H. Aboul Wafa. *J. Trop. Pediat.* 3: 17, 1957.

These authors have studied the pancreatic activity in various syndromes of malnutrition and compared this finding with the average normal findings in a similar age group. All cases were submitted to duodenal intubation, and the juice obtained was examined for (a)

color (b) pH, (c) tryptic activity, (d) diastatic index, and (e) any abnormal constituent.

The material studied comprised 19 normal infants, 9 cases of kwashiorkor, 4 cases of marasmus, and 3 cases of "growth failure syndrome" (the latter characterized by a retardation of weight, height, and development, with an approximately normal body constitution). All cases of severe kwashiorkor showed scanty duodenal juice with excess mucin, absent tryptic activity, and diminished or normal amylase. Trypsin started to diminish very early, before the development of liver enlargement, edema, or dermatosis. In marasmic infants the duodenal juice was scanty, tryptic activity was absent, but the amylase was normal. Infants with "growth failure syndrome" showed normal pancreatic activity. J. WATERLOW

A Neuropathy in Children Recovering from Malnutrition (Kwashiorkor). E. Kahn. *Central African J. Med.* 3: 398, 1957.

Three cases are reported of a neurologic syndrome related to the recovery phase of infantile malnutrition. The syndrome consists mainly of extrapyramidal components, such as tremors and postural abnormalities. Pyramidal tract involvement is slight and less constant. Complete recovery from the syndrome seems to be the rule.

These manifestations are similar to others described in the literature. The cause is obscure. It is not encephalitis and probably is distinct from the portal-systemic encephalopathy found in adults. Deficiency of certain vitamins, particularly A, D, C, B_{12}, nicotinamide, riboflavin, pyridoxine, and pantothenic acid, can be excluded because some of the children were receiving these substances when the tremors began. Administration of methionine and glutamic acid, as well as the intravenous injection of glucose and calcium, did not influence the course of the syndrome. Laboratory tests were within normal limits. Urine specimens did not contain abnormal amounts of amino acids.

It is likely that this syndrome is identical with "acute cerebral tremors" described in 1909 by Zappert. This is an interesting clinical observation and deserves further study. S. O. WAIFE

Elevations of serum lipids in starvation states after refeeding may represent the result of rapid release of fat and cholesterol from the liver. However, it is necessary to examine the rate of utilization of lipids under these conditions using labeled fats.

The Serum Lipids in Kwashiorkor. R. Schwartz and R. F. A. Dean. *J. Trop. Pediat.* 3: 23, 1957.

In 20 children admitted to the ward of the Infantile Malnutrition Group at Kampala, Uganda, the serum levels of neutral fat, phospholipids, and free and esterified cholesterol were studied. It was noted that soon after the beginning of treatment there were large increases in the level of neutral fat and esterified cholesterol, with a subsequent decline. It is suggested that the initial rise is associated with mobilization of fat and cholesterol from the liver, and the fall in the amount of neutral fat later in the course of treatment may be associated with utilization of fat in the normal manner. The theory is put forward that in kwashiorkor the failure to mobilize fat may be more significant than the mere presence of fat in the liver. J. WATERLOW

Sporadic reports of kwashiorkor in adults due to protein deficiency attest to the more general recognition of this syndrome.

"Kwashiorkor" in an Adult. D. M. Krinkler and V. Schrier. *Lancet* 1: 510, 1958.

A case is described in detail of a 37-year-old man who had a side-to-side anastomosis of a loop of small bowel, found to be obstructed at laparotomy three years after a subtotal gastrectomy. For two years following the anastomosis the man's health deteriorated until he was severely ill. He had lost 63 pounds and was very weak; his hair became reddish and stopped growing. Serum albumin was 1.2 g and globulin 1.8 g/100 ml; hemoglobin was 8.8 g/100 ml. Medical treatment was unsuccessful, and retrobulbar neuropathy and peripheral neuritis developed.

On readmission a blind loop was diagnosed and the patient was prepared for operation by blood transfusion and a high-calorie diet. He was "ravenous," eating food to the value of 10,000 calories on "an average day." A six-foot blind loop was found at operation and the short circuit was closed. Postoperatively he made a dramatic and uninterrupted recovery. F. E. HYTTEN

A Kwashiorkor-Like Syndrome Observed in Monkeys Fed Maize. R. H. Follis, Jr. *Proc. Soc. Exper. Biol. & Med.* 96: 523, 1957.

Male and female growing monkeys (*Ceropithecus griseoviridis* or *aethiops*) were fed ad libitum a basic diet of unenriched ground yellow cornmeal containing per 100 g dry weight 10.2 g protein, 7.6 g lipid; 1.04 g ash; 55 mg calcium; 215 mg phosphorus; 0.72 mg ascorbic acid; 0.50 mg thiamine; 0.18 mg riboflavin; and 230 I.U. vitamin A, with an occasional supplement of sugar and ascorbic acid. Water was available at all times. Eight animals were thus maintained up to 41 weeks. One animal received a commercial ration supplemented with vitamin C and three additional monkeys were fed rice supplemented with ascorbic acid. The animals kept on the diet of maize disclosed failure of growth, loss of weight, weakness, apathy, edema with hypoalbuminemia, and fatty infiltration of the liver. The latter change, which on the basis of liver biopsies was found to be present already after seven weeks, spread from the periportal areas and ultimately involved the entire lobule. The findings resemble those observed in children suffering from kwashiorkor.

M. SILBERBERG

There have been various opinions expressed concerning the anemia of kwashiorkor. The anemia may have several etiologies, depending on the presence or absence of infestations, the amount of dietary iron available, and the type of diet responsible for the malnutrition syndrome.

The Bone-Marrow Picture of Kwashiorkor in Djakarta. K. Lien-Keng, S. D. Poesponegoro, and P. S. Hin. *Doc. Med. Geog. Trop.* 9: 69, 1957.

The blood picture and bone marrow are described in 50 cases of kwashiorkor and illustrated by excellent photographs. The hematologic indices and the cell counts in the marrow are set out for each case in two large tables.

The marrows were mostly normoblastic; a few showed megaloblasts, intermediate megaloblasts, or giant proerythroblasts. The most striking finding was a decrease in cellularity, particularly of the erythropoietic system, with an increase in fat and fixed cells. The myeloid-to-erythroid ratio was raised. In some cases there were pathologic granulocytes and megakaryocytes.

The response to treatment is not considered in this paper. The etiology is discussed in general terms. No single causal factor or deficiency can be incriminated. The authors suggest that liver damage may be an important cause of bone-marrow insufficiency in kwashiorkor. Endocrine imbalance and a disturbance of enzyme systems may also play a part. J. WATERLOW

Intramuscular Iron in the Treatment of the Anaemia Associated with Kwashiorkor. H. C. Trowell and M. J. Simpkiss. *Lancet* 2: 265, 1957.

Anemia is a frequent accompaniment of kwashiorkor and, although it has been labeled a protein-deficiency anemia and usually shows few of the usual criteria of iron deficiency, dietary treatment without hematinics may not correct the anemia. In some cases the hemoglobin level in the peripheral blood falls during treatment with high-calorie and high-protein diet and a transfusion may be necessary. Treatment with oral iron has not been satisfactory.

In 17 cases of typical kwashiorkor admitted to the hospital within a two-month period, 13 were given intramuscular Imferon in addition to routine dietetic treatment. Of the 4 excluded, 1 had typhoid fever, 2 died soon after admission, and 1 was so anemic from hookworm infestation as to require transfusion.

Except for 2 cases with an initially normal hemoglobin level, the treated group had a uniformly satisfactory response, the average hemoglobin rising from an initial level of 7.9 to 10.6 g/100 ml in 23 days. The mean maximum reticulocyte response was about 20 per cent at about the eighth day. F. E. HYTTEN

Differences of opinion expressed by investigators on the effect of antibiotics upon growth rates of malnourished children may reflect the variations in pathogenesis. Where infection is a problem, the use of antibiotics may improve the nutrition status by eliminating this factor.

The Effect of Aureomycin on Undernourished African Children. L. G. MacDougall. *J. Trop. Pediat.* 2: 74, 1957.

Antibiotics have been found of value in increasing growth rates and eliminating infections in animals. It was therefore thought justifiable to assess their use in undernourished children in Nairobi, where the major clinical problems presented in these cases are (a) difficulty of establishing a suitable mixed diet, (b) failure to gain weight, with recurrent diarrhea, and (c) a high rate of cross infection.

Seventy-two children were studied whose average age was 2 years. Of these, 38 children received Aureomycin 50 mg daily, and a control group of 34 received placebos. Those children on Aureomycin showed an average daily weight gain of 45.3 g as compared with 14.1 g in the controls. The Aureomycin-treated group also showed an improved general nutritional status, appetite and mental well-being as compared with controls.

There was a significant increase in the total serum protein, albumin, and hemoglobin in the Aureomycin-treated group. There was also a lower incidence of cross infection and a shorter duration of nonspecific diarrhea. No untoward side effects were noted as the result of Aureomycin administration. J. WATERLOW

The response to protein feeding has been described as rapidly favorable where irreversible hepatic and other visceral involvements have not developed. Since there are no differences in the rate of response with the type of protein employed, skimmed milk powder has been the most practical approach to the problem of supplying an adequate protein intake.

Influence of High-Protein Diets on Liver-Function Tests in Kwashiorkor. A. A. Kinnear and P. J. Pretorius. *Brit. M. J.* 2: 389, 1957.

It has been previously shown by these authors that tests of liver function are mostly of little value for either diagnosis or prognosis in kwashiorkor. Serum albumin is always low, however, and bromsulphthalein retention almost always raised.

In the present study, the effects are shown of different high-protein diets (previously described by Brock *et al.*, *Lancet* 2: 355, 1955) on liver-function tests during recovery.

There were no differences in the efficacy of the different diets. Serum albumin rose rapidly and progressively, and serum globulin also showed a progressive rise. BSP retention fell quickly in the first three days to normal levels and continued to decrease slightly thereafter. Nothing of value could be learned from the other liver-function tests. F. E. HYTTEN

A Five Year Follow-up of Coloured Children with Kwashiorkor in Cape Town. P. V. Suckling and J. A. H. Campbell. *J. Trop. Pediat.* 2: 173, 1957.

In a follow-up study of 27 cases of kwashiorkor in colored children in Cape Town, it was found that despite

a return to poor surroundings, children in this area generally make a good recovery. There is no evidence of permanent damage. Growth in height is maintained at the same rate as controls, and, although at a lower level, it does not differ statistically from these controls. Growth in weight shows a recovery two years after the initial admission for malnutrition, and thereafter progresses at the same rate as controls. Anemia is corrected within five years. Follow-up liver biopsies show no evidence of cirrhosis. J. WATERLOW

MAGNESIUM DEFICIENCY

The principal concentration of magnesium in body tissue is within the skeleton. However, its function as an enzyme activator is of greater physiologic significance. Phosphatases and peptidases and reactions involving adenosinetriphosphate require this ion for maximal activity. With a decrease in plasma magnesium concentration, tetany, tremors, and convulsions occur. Clinical states in which magnesium concentrations are reduced include hepatic cirrhosis, diabetic coma during treatment, diarrheal states, and hypoparathyroidism.

Symptomatic Magnesium Deficiency in Man. J. F. Hammarsten and W. O. Smith. *New England J. Med.* 256: 897, 1957.

The symptoms of a well-documented case of magnesium deficiency are described. The patient had intermittent diarrhea for two years before admission to the hospital. There was a large loss of body fluids and parenteral fluid therapy without added magnesium was given. After 52 days in the hospital the patient became confused and displayed slight generalized tremors. He finally became stuporous, showed pronounced flapping tremors, twitchings, and athetoid movements. When magnesium was administered these symptoms disappeared. When the therapy was discontinued the tremors again reappeared and the patient became confused. Recovery followed magnesium therapy.

The authors believe that as soon as a simple clinical determination for magnesium is developed more cases of magnesium deficiency will be recognized.

M. W. BATES

The improvement in abnormal lipoprotein patterns of patients with coronary disease upon administration of magnesium reported below requires further study. It is interesting to recall in this connection that the ratio of bound to unbound magnesium is altered in hypo- and hyperthyroidism. The latter conditions appear to have a direct effect upon lipoprotein metabolism. Conceivably, there may be a relationship between the serum magnesium partition and the lipid distribution.

Correlation of Serum-magnesium and Serum-cholesterol Levels in South African Bantu and European Subjects. I. Bersohn and P. J. Oelofse. *Lancet* 1: 1020, 1957.

It has been shown that parenteral magnesium sulfate causes a dramatic clinical improvement in cases of coronary thrombosis or insufficiency and in many cases corrects the abnormal lipoprotein patterns.

In 47 normal Europeans whose mean serum cholesterol concentration was shown to be about 215 mg/100 ml, the serum magnesium was 1.92 ± 0.15 mg/100 ml; in 53 normal Bantu (mean serum cholesterol about 170 mg/100 ml or less) the mean serum magnesium level was 2.11 ± 0.19 mg/100 ml.

The difference between the groups is highly significant. In another group of 80 Europeans a highly significant (negative) correlation is shown between the serum cholesterol and serum magnesium levels.

This paper is a preliminary communication and the findings are not discussed. F. E. HYTTEN

Difficulties with analytical procedures for magnesium have retarded progress in this field in the past. Newer methods for study of this element in human nutrition are being developed.

Preparation and Bioassay of a Low Magnesium Liquid Diet for Human Consumption. B. A. Barnes, G. G. Eddison, and O. Cope. *Surgery* 42: 643, 1957.

Barnes and his associates have devised a diet very low in magnesium as a preliminary to studies of the metabolism of this element in man. Magnesium is almost universally present in moderate concentration in the usual foodstuffs. Accordingly, the authors concentrated on the formulation of a simple, but nutritionally adequate and palatable, liquid diet containing a minimum number of ingredients from which magnesium could be readily removed. The basic feature of their method is the processing of milk products with a cation exchange resin. The composition of the resultant material can then be altered by the selective addition of various minerals. Chemical analyses of their basic diets revealed magnesium contents of less than 0.12 meq/l or about 1 p.p.m. of magnesium by weight. Biologic confirmation of the specific deficiency was demonstrated in rats. STANLEY M. LEVENSON

WATER METABOLISM

The nutritional requirement for water is that amount which is required to replace the normal obligatory losses. The normal losses include water required for renal excretory processes, vaporization through respiration, sweating, and the moisture in stools amounting to approximately 2,500 cc daily. Water intake is regulated by the sensation of thirst which is stimulated through hypothalamic receptors.

Adipsia Produced by Hypothalamic Lesions in the Rat. D. G. Montemurro and J. A. F. Stevenson. *Canad. J. Biochem. & Physiol.* 35: 31, 1957.

In female rats of the Sprague-Dawley strain, bilateral electrolytic lesions were produced in the lateral hypo-

thalamus. Subsequently food and water intake were observed in these animals, and the brain lesions were studied microscopically. Hypodipsia was observed in those animals in which the lesions were placed in the lateral hypothalamic areas at about the plane of the posterior ventromedial nuclei and the anterior border of the premammillary bodies. M. SILBERBERG

The moisture content of solid foods supplies water to the body amounting to 600 cc, more or less. In addition, oxidation of absorbed foodstuffs produces approximately 400 cc of water.

Gastrointestinal Regulation of Water and Its Effect on Food Intake and Rate of Digestion. S. Lepkovsky, R. Lyman, D. Fleming, M. Nagumo, and M. M. Dimick. *Am. J. Physiol.* 188: 327, 1957.

An investigation was undertaken to determine the effects of water deprivation during meals in rats. Food intake, water content of gastrointestinal solids, rate of digestion, and tissue water content were studied. Rats fed without water ate less food than did rats fed with water. The gastric contents of all animals fed with or without water was approximately 40 per cent water and indicates close regulation of water in the gastric contents. When fed without water, rats regulate their food intake so that it matches the amount of water that they can mobilize from their own tissues, thereby maintaining the proper water-to-food ratio in the gastric contents. How this is reflected in the mechanisms that control food intake is unknown. The water found in the gastrointestinal contents of rats fed without water is furnished by selected tissues, especially the skin, probably the adipose tissues and perhaps other tissues. The contents of the intestinal lumen contains about 76 per cent of water in all the rats irrespective of the availability of water with meals. The total solids in the intestinal lumen of rats eating without water averaged 0.39 g and 0.52 g for the rats eating with water. The regulation of both water and solids in the intestinal lumen indicates that it acts as though it were a part of the internal environment. Withholding of water during meals does not appear to interfere with digestion but it definitely decreases appetite and effects a reduction of food intake. AUTHORS

Transfer of Water and Solutes by an In Vitro Intestinal Preparation. D. H. Smyth and C. B. Taylor. *J. Physiol.* 136: 632, 1957.

The authors describe a new type of intestinal preparation which will transport water from the mucosal to the serosal surface. Glucose, oxygen, hydrostatic and osmotic pressures, and temperature play a role in this transfer. Metabolic inhibitors prevent the transfer of water. Alanine, glucose, and lower fatty acids are concentrated as they pass through the intestinal wall. The concentration of sodium and *d*-alanine is unchanged. Chloride, creatinine, and urea are passed through the wall and appear on the serosal side in a lower concentration. These experiments suggest that fluid transfer is an active process. M. J. OPPENHEIMER

In addition to the antidiuretic hormone of the hypothalamico-hypophyseal system, the rate of water excretion by renal tubular activity is governed by osmotic vectors influencing cellular activity.

The Influence of Bodily Hydration on the Renal Concentrating Process. F. H. Epstein, C. R. Kleeman, and A. Hendrikx. *J. Clin. Invest.* 36: 629, 1957.

Studies on hydration were performed on normal young men. Various renal function and metabolic studies were performed which led to the results indicating that chronic underhydration, as well as prolonged forcing of fluids, drastically modifies the ability of the kidneys to reabsorb water and to concentrate solutes in the urine. It would appear that the state of hydration of tissues including, and perhaps most important, the cells of the distal and collecting tubules themselves may be the factors conditioning renal concentration.

S. O. WAIFE

The water requirements during parenteral fluid therapy are of extreme importance, as is the maintenance of electrolyte balance. In children whose kidneys are less adaptable or in those with renal disease considerable care must be exerted to avoid exceeding their capacity to concentrate or dilute the excreted solutes.

The Maintenance Need for Water in Parenteral Fluid Therapy. A. Holliday and E. Segar. *Pediatrics* 19: 823, 1957.

Since losses of water are a function of expenditure of energy, needs for water must be computed from some function of energy metabolism. A scheme for estimating total expenditure of energy from weight alone is presented with means of calculating daily needs for the average hospitalized patient as follows: 0–10 kg, 100 cal/kg; 10–20 kg, 1,000 cal + 50 cal/kg for each kg over 10 kg; 20 kg and over, 1,500 cal + 20 cal/kg for each kg over 20 kg. Comparison with other methods—surface area, calories (Darrow *et al.*), calories (Wallace)—reveals close agreement, with the exception of computing water needs on the basis of surface area in the 6–15 kg weight range. Here the values are significantly less than estimated by other methods. This is due to the fact that energy expenditure, basal or total, is higher per unit of surface area for the child of intermediate weight than for the small infant or adult. An increase of about 50 per cent in needs for water per unit of surface area for the group would make them comparable to other groups.

For all ages, insensible loss of water (IWL) in the resting state in a comfortable environment is a constant function of basal energy expenditure and is about 45 ml for each 100 cal of energy. At this level, 25 per cent of the total expenditure of energy is dissipated by insensible loss of water. With increased activity, infants

show a pronounced increase in IWL per 100 cal. In hospitalized patients, estimates vary from 750 ml/m² for adults (Newburgh *et al.*) to 930 ml/m² for all ages (Heeley and Talbot). The latter showed that IWL per unit of surface area was greatest in infancy and diminished with age. By recalculation of data in these reports, the authors express IWL as 50 ml/100 cal/day.

Solute excretion in infants receiving glucose and water averages 15 mOsm/100 cal/day. The minimum solute excretion appears to be 10 mOsm/100 cal/day and maximum 40 mOsm. Extra electrolyte usually included in parenteral fluid therapy increases the average figure to 25 mOsm. Calculation involving these data and consideration of glomerular filtration rates indicate that 66.7 ml of water for renal excretion would permit (1) the solute load of 10 to 40 mOsm/100 cal/day to be excreted between the concentrations of 150 and 600 mOsm/l; and (2) the average solute load of 25 mOsm/100 cal/day to be excreted at a concentration of 375 mOsm/l. Random observations on urinary solute concentration during parenteral fluid therapy in 28 infants, 25 children, and 8 adults indicate that the amount of fluid actually given did not consistently permit excretion of solutes within a safe concentration, as it imposed demands on dilution and concentration of solutes which might well exceed individual capacity. This was more evident among the infants. It is important that daily water needs be administered over a period of at least 12 hours and preferably continually, especially in infants.

The average figure for total loss of water is 116.7 ml/100 cal/day. Water of oxidation will provide nearly 16.7 ml. The balance, 100 ml/100 cal/day, must be provided parenterally. Fortunately, average needs for water expressed in ml equals estimated energy expenditure in calories. Maintenance requirements of sodium, chloride, and potassium are 3.0, 3.0 and 2.0 meq/100 cal/day, respectively. T. C. PANOS

LATHYRISM

The growth of cartilage was found to be altered when sweet-pea seeds (Lathyrus odoratus) *were placed in the diet of growing rats. The active principle responsible for these alterations has been found to be β-aminopropionitrile. Within 24 hours of administration of these substances the cartilage cells lose their orderly arrangement and proceed to form thick bands of disorganized columns. The matrix becomes soft and pulpy. The matrix of cartilaginous structures and major vessels is weakened, resulting in skeletal deformities and vascular dilatation.*

Experimental Lathyrism in Mice Fed Diets Containing Sweet Peas or β-aminopropionitrile. W. Dasler and R. V. Milliser. *Proc. Soc. Exper. Biol. & Med.* 96: 171, 1957.

Lathyrism was studied in Swiss mice and compared with that established for the rat. Weanling males were fed a stock diet supplemented with 50 per cent sweet peas or 0.2 to 1 per cent β-aminopropionitrile. Since a high-casein diet protected rats against lathyrism, a number of mice were kept on the lathyrism-producing diet supplemented with 10 per cent casein. Mice were by far less susceptible to lathyrism than rats and showed remarkable individual variations in their response. While all rats fed 0.2 per cent β-aminopropionitrile for two to three weeks had developed aneurysms and skeletal deformities, only a few mice treated with the same dose disclosed manifestations of lathyrism, even if treatment was continued for four to seven weeks. The incidence and severity of the lesions in mice could be increased by administration of the high doses. Paraphimosis could also be produced by high doses. However, the paralysis and urinary retention common in rats were not observed. A high-casein diet failed to attenuate the course of lathyrism in mice.

M. SILBERBERG

The attenuation of the lesions of lathyrism by administration of triiodothyronine provides a clue as to the possible enzymatic reactions affected by the toxic agent.

Prevention of Aminonitrile Lesions in Rats with L-Triiodothyronine. I. V. Ponseti. *Proc. Soc. Exper. Biol. & Med.* 96: 14, 1957.

Weanling male rats of the Sprague-Dawley strain were fed ad libitum ground Purina chow containing 0.06 or 0.075 per cent of β-aminonitrile in order to produce lathyrism. The animals thus fed served as controls. Other groups of rats received supplements of 0.25, 0.5, 1.25, or 10 mg/100 g diet of L-thyroxin or 0.02, 0.06, 0.1, or 0.25/100 g diet of 3,5,3′-L-triiodothyronine. Some animals were fed a combination of triiodothyronine and thyroxin in varying doses. After 17 days the changes in the long bones, in particular the changes in the epiphyseal growth zones, periosteum, and ileum, were studied microscopically. Low doses of L-triiodothyronine suppressed the mild forms of aminoacetonitrile poisoning, whereas thyroxin had to be administered in much higher doses in order to show the same protective effects. It was estimated that L-triiodothyronine when given orally was over 100 times more effective in attenuating the conditions than was L-thyroxine, and when administered parenterally the former substance was 50 times more effective than the latter.

M. SILBERBERG

Effect of Beta-Aminopropionitrile on Reproduction of Chickens. B. D. Barnett, D. J. Richey, and C. L. Morgan. *Proc. Soc. Exp. Biol. & Med.* 95: 101, 1957.

Diets containing *Lathyrus odoratus* seeds are known to induce skeletal abnormalities, hernias, aortic aneurysms, and reproductive failure. However, different species show different susceptibility to the lathyrus factor. In turkeys, which are more sensitive than rats, nerve damage and internal hemorrhages were more marked than the skeletal changes. The various changes are probably due to an interference of β-aminopropioni-

trile (BAPN) with the calcium metabolism. In order to test this concept further, white Leghorn hens were fed, respectively, 0.03 per cent or 0.06 per cent BAPN for four weeks. Subsequently, the animals received a stock ration. Egg production went down to 12 per cent of the normal at the high level of BAPN feeding and to 29 per cent at the low level of supplementation with BAPN in the ration. In addition, the eggs were deformed and had soft shells. Between 40 and 80 per cent of the embryos showed hemorrhages. If BAPN was discontinued, normal conditions were gradually restored as far as egg laying and shell formation were concerned. M. SILBERBERG

The extensive distribution of the lesions in a variety of tissues is indicative of the diffuse action of the agent upon fibroblasts and matrix materials generally. These changes might be studied effectively by means of the S^{35} sulfate label in the formation of sulfomucopolysaccharides.

Elastic Fiber Alterations in Rats Treated with Lathyrus Odoratus: Histopathological Study of Elastic Cartilage and Elastic Fibers in Arteries and Membranes with Special Reference to the Occurrence of Extra-aortic Dissecting Aneurysms. D. G. Walker. *A.M.A. Arch. Pathol.* 64: 434, 1957.

Weanling rats were fed for 2 to 4 weeks a synthetic diet to which equal amounts of sweet pea meal were added. The changes occurring in the elastic fibers, particularly in abdominal vessels, intestine, and cartilage of the external ear, were studied. In addition to the known formation of dissecting aneurysms of the aorta and skeletal deformities, a number of small aneurysms and diverticula were found. The main change consisted of a remarkable decrease of elastic fibers, with petechial hemorrhages in the vessel walls and the elastic cartilage. Associated with these changes were proliferation of fibroblasts, increase in collagenous fibers, and decrease of periodic acid–Schiff-positive material. Since these changes cannot be produced in animals older than seven weeks, one has to deal with a deficiency in elastinogenesis rather than destruction of elastic tissue in the animals fed the lathyrus factor.

M. SILBERBERG

Acid Mucopolysaccharides in the Histopathogenesis of Aortic Aneurysms in the Lathyrus-Fed Rat. Z. T. Wirtschafter. *A.M.A. Arch. Path.* 64: 577, 1957.

The histogenesis of aortic lesions in lathyrism was analyzed with special reference to the changes taking place in the ground substance of the aorta. Weanling rats of the Long-Evans strain received a stock diet to which equal parts of finely ground seeds of *Lathyrus odoratus* were added. The experiments were extended until the rats had reached an age of from 6 to 9 weeks. It was found that the change leading to dissecting aneurysms were of generalized and not of local nature, since the tissue changes were observed at a distance from the site of the formation of the aneurysms. Throughout the length of the aortas the following changes were observed: increased amounts of acid mucopolysaccharides, elastolysis, hyperplasia and hypertrophy of fibroblasts, hypertrophy of the elastic lamina, loss of elastic interlaminar fibrils, and hypertrophy of the adventitia.

M. SILBERBERG

The weakening of fibrous tissues, bone matrix, and cartilage by the lathyrus factor may permit skeletal deformities and exostoses to develop, through the tension and pull exerted by muscular contraction. This interpretation is supported by the second of the abstracts below and would tend to oppose the conclusions deduced in the first.

Histology of Lathyrus-Induced Exostoses of Rats: The Initial Changes at Tendon-Bone Junction. V. L. Yeager and C. J. Hamre. *A.M.A. Arch. Pathol.* 64: 171, 1957.

Female albino rats weighing from 176 to 288 g were fed a diet composed of equal amounts of Purina laboratory chow and meal of *Lathyrus odoratus* in ad libitum quantities. The animals were sacrificed after periods of from 1 to 14 days. The early stages of formation of exostoses produced under these conditions at the insertion of the pectineus and adductor longus muscles were studied microscopically. The muscles and cortex of the femurs remained unchanged and did not contribute to the formation of exostoses, but the latter arose from the inner periosteal layer. Fibrous tissue masses began to form after one day and continued to increase in amount until the end of the first week. From this nucleus, osseous tissue developed by way of intramembranous ossification. Apparently one has to deal with hyperplastic growth of the periosteum stimulated by the lathyrus factor. M. SILBERBERG

Influence of Denervated Muscles on Exostoses of Rats Fed a Sweet-Pea Diet. C. J. Hamre and V. L. Yeager. *A.M.A. Arch. Path.* 65: 215, 1958.

In adult female rats made lathyric by feeding a diet composed of equal amounts of Purina laboratory chow and meal of the sweet pea, *Lathyrus odoratus*, the influence of muscle activity on the development of exostoses and skeletal deformities of femurs and pelvis was studied. Unilateral transection was performed of the nerves supplying the adductor longus, of the femoral and obturator nerves, and of the nerves originating in the roots of the lumbar plexus. The bones of the uninjured contralateral extremity served as controls. Denervation and ensuing atrophy of the muscles inhibited or prevented the formation of exostoses and skeletal abnormalities in most experimental groups. It seems therefore that muscle tension is an essential factor in the evolution of the bone lesions in the lathyric rat. M. SILBERBERG

ITEMS OF GENERAL INTEREST

Skin Turgor as a Quantitative Index of Dehydration in Children. Z. Laron. *Pediatrics* 19: 816, 1957.

Quantitative measurements of skin turgor were made in patients with diarrhea and with water deprivation, before and 12 and 24 hours after fluid therapy was begun. Weight, serum electrolytes, and blood nonprotein nitrogen were also determined. Most of the patients were infants. Loss of skin turgor was greater and was observed with less weight loss in the diarrhea patients than in those deprived of water. In primary water depletion, there was no loss of normal skin elasticity until a weight loss of at least 6 per cent occurred, whereas in the diarrhea group, detectable decrease in skin turgor was observed with a weight loss of 2.5 per cent. There was no over-all correlation between concentrations of sodium in the serum and loss of weight among the children with diarrhea, although it appeared that the smaller losses of weight were associated with a lower concentration of sodium in the serum. In the group with water deprivation there was a linear correlation between serum sodium concentration and weight loss. The concentration of NPN was higher in the patients with diarrhea for any given degree of dehydration. In both groups, there was an over-all correlation between NPN concentration and weight loss. In the diarrhea patients, there was no correlation between concentrations of sodium and NPN.

Any change in the water of the skin is largely of extracellular water and skin turgor is mainly a function of the hydration of the extracellular compartment. In water deprivation, the water loss from the intracellular and extracellular compartments is roughly proportional to their volumes, so that one-third of the loss comes from extracellular and two-thirds from intracellular sources. In salt depletion, the deficit is sustained to a greater extent by the extracellular fluid and this compartment may bear one-half to two-thirds of the total water loss. The finding of essentially normal skin turgor in certain cases of diarrhea in which water loss exceeds electrolyte loss is thus partially explained at least. The finding of normal skin turgor in cases of diarrhea in which dehydration is suspected by history or weight loss should suggest the possibility of hyperelectrolytemia.

T. C. Panos

The Electrolyte Content of the Sweat in Fibrocystic Disease of the Pancreas. B. W. Webb, P. T. Flute, and M. J. H. Smith. *Arch. Dis. Childhood* 32: 82, 1957.

Specimens of sweat were obtained from 12 patients with fibrocystic disease, varying in age from 11 months to 6 years. All 12 were proved cases in each of which pancreatic enzymes had been shown to be absent by at least one duodenal ospiration. The control series consisted of 20 ward patients varying in age from three months to six years with no disease referable to the gastrointestinal tract. Filter papers were attached to the child with plastic strips over the back and the child placed in a plastic bag tied loosely around the neck and allowed to lie covered with three or four blankets for 1–2 hours. The results fully confirmed the report of Di Sant' Agnese *et al.* (*Pediatrics* 12: 549, 1953). It was concluded that sodium and chloride levels above 70 meq/liter in sweat specimens collected according to the method described, together with typical clinical findings, are diagnostic of fibrocystic disease. However, adherence to the details of collection is important in that electrolyte content of sweat in any individual varies with a number of factors such as the area of collection, nature, and intensity of the stimulus to sweating, environmental temperature, dietary intake, and adrenocortical activity. The mean electrolyte content was sodium 125 meq/liter of sweat and chloride 127 meq/liter. The authors state that the modification they described in collection of the specimen improves the accuracy of collection and determination of these electrolytes.

T. C. Panos

The Toxicity of Low-Molecular Triglycerides. A. Wretlind. *Acta physiol. scandinav.* 40: 338, 1957.

Low-molecular triglycerides in the form of emulsions were administered intravenously to mice. The LD50 was observed to be lowest for triisovalerin. When the chain contained less than five it increased, being 1,600 ± 81 mg/kg for triacetin as compared to 82 ± 4 for triisovalerin. Above five carbon atoms it rises progressively above 10,000 mg/kg for trinonylin, tricaprinin, and triundecylin.

M. J. Oppenheimer

Radiation from Strontium^{90} Not Found in Milk in Harmful Amounts. G. P. Whitlock. *J. Dairy Sci.* 40: 592, 1957.

The author prepared this statement from information received from the Division of Biological and Medical Research, Argonne National Laboratory. It is true that all foods containing calcium may carry strontium^{90}, which may eventually reach the bone structure of the human body. Increased amounts of strontium^{90} have been detected in our milk supply, probably arising from nuclear fall-out to soils which contaminate the plants eaten by the milk-producing animals. However, it is known that the radiation level from strontium^{90} reaching human beings in the United States from all sources, food and non-food, is less than one per cent of the amount that would be harmful. Long before "man-made" sources of radiation existed, the human race has been exposed to radiation from cosmic rays and, in certain areas, from radioactive minerals. It should be a long time before fall-out radioactivity can catch up to that to which we have been exposed heretofore. Precise methods are in use for determining the presence of radioactivity. These methods are so accurate that it is possible to detect and measure the presence of less than one ten-thousandth of the amount of radioactive strontium which has been declared safe. The consumer may depend on it that scientists will continue to be alert to the possibility of danger.

F. E. Rice

Protective Effect of a Sucrose Diet in Mercuric Chloride Poisoning. A. Surtshin. *Am. J. Physiol.* 190:271, 1957.

Rats fed only sucrose and vitamins for three weeks or more usually survive intravenous injection of 3 mg/kg of mercuric chloride, a dose lethal for rats on a normal diet. Survivors returned to a normal diet grow rapidly and appear grossly normal. Survival occurs in the presence of a diminished rate of excretion of radiomercury and a renal concentration and content of radiomercury higher in sucrose-fed protected rats than in unprotected rats on a normal diet. Sucrose feeding itself causes slower excretion of mercury; evidence indicates that the renal binding of mercury in protected rats is greater than in the unprotected. Some sucrose-fed rats surviving an initial dose of mercuric chloride, survive additional doses after return to a normal diet. The excretion and renal content of mercury is not altered by ammonium chloride acidosis in chow-fed rats given mercuric chloride.

AUTHORS

The Adrenal Cortical Response to Surgery. I. The Effect of Anesthesia on Plasma 17-Hydroxycorticosteroid Levels. R. W. Virtue, M. L. Helmreich, and E. Gainza. *Surgery* 41:549, 1957.

A transient increase in adrenal cortical activity (as reflected principally by increases of certain steroids in the adrenal vein plasma, peripheral plasma, and urine) is usual after injury and operation. In general, the response is roughly proportional to the severity of the trauma or operative procedure. Since anesthesia is an invariable accompaniment of surgical operations, Virtue and his colleagues have assessed the effects of some commonly employed anesthetic agents on adrenocortical function of seventy patients. Their index was the levels of free 17-hydroxycorticosteroids in the plasma. Twenty-nine of these patients were males and 41 were females; they ranged in age from 5 to 81 years and had a variety of diseases. The studies were begun in the morning in an attempt to equate the variable of the normal diurnal cycle of plasma 17-hydroxycorticosteroid concentration. Plasma samples were collected before induction, after one hour of inhalation of anesthesia or about one-half hour of spinal anesthesia, and after one hour of surgery.

"Four anesthetic groups were studied: (a) 35 patients in whom anesthesia was maintained with ether, following a five- to ten-minute period of induction with thiopental plus cyclopropane (14 cases), cyclopropane (11 cases), or nitrous oxide (10 cases); (b) 15 patients were given thiopental sodium plus nitrous oxide throughout; (c) 10 patients were given cyclopropane; and, (d) 10 patients received spinal anesthesia (Pontocaine). In groups (a), (b), and (c) inhalation anesthesia was maintained for one hour prior to surgery. Since it was not possible to allow a full hour of spinal anesthesia before surgery in group (d), the duration of these studies varied from 15 to 45 min (average: 27 min).

"The surgical operations performed varied from minor to extensive major procedures. However, in all anesthetic groups, there were procedures of sufficient magnitude to permit evaluation of the effects of one hour of surgical trauma on plasma 17-hydroxycorticosteroids."

There was a statistically significant rise in the mean plasma free hydroxycorticosteroid concentrations of the patients receiving ether (15 of the 35 patients), but no significant changes in the other groups. In contrast, there was a significant rise of this plasma component in all groups, except that receiving spinal anesthesia, after one hour of surgery. The authors were unable to determine, from an examination of the clinical aspects of the patients, why some patients receiving ether responded with an apparent increased adrenocortical activity while others did not.

In a portion of the patients (15 who received ether and nine maintained on thiopental-nitrous oxide or cyclopropane) the plasma levels of the glucuronic acid conjugated 17-hydroxycorticosteroids were measured simultaneously with the free; parallel values were found—but in only three of these were there significant rises in either. During surgery, a marked increase in the plasma free 17-hydroxycorticosteroids occurred in all, followed by a rise in the conjugated compounds; the response was similar in both groups.

S. M. LEVENSON

Ureteroileal Anastomosis. T. A. Stamey and W. W. Scott. *Surg. Gynec. & Obst.* 104:11, 1957.

Among the undesirable complications of ureterosigmoidostomy are hyperchloremic acidosis, hypokalemia, pyelonephritis, hydronephrosis, weight loss, and weakness. Dissatisfied with these, Stamey and Scott turned to ureteroileal anastomoses, using an isolated ileal segment. Their results on 14 patients operated on during the preceding year are gratifying. Thirteen patients are alive and well, with continuing normal or improving renal function and morphology. There was one instance of transient pyelonephritis seven months postoperatively in a patient; this responded promptly to antibiotics. No abnormalities in serum electrolytes have been observed; urinary output has always been less than the fluid intake. Included in the series were two patients who had ureterosigmoidostomy five years earlier. Improvement in appetite, marked weight gain, and increased strength followed transplantation of the ureters from the sigmoid to the isolated ileal segment. The one patient who died was a 71-year-old man who died on the tenth postoperative day from a pulmonary embolus.

S. M. LEVENSON

Separation of Bone Sodium, Potassium, and Calcium by the Use of Cation Exchange Resin. N. Norman, J. C. Beck, and J. S. L. Browne. *J. Lab. & Clin. Med.* 50:308, 1957.

Greater interest in an improved determination of sodium and potassium in bone has followed the establishment of the important role of the bone system in

sodium and potassium metabolism of the body. The difficulty of the methodology has been due to the high concentration of calcium in relation to the concentration of sodium and potassium—e.g. 200:4:1, respectively—with calcium as milligrams of secondary phosphate, but with sodium and potassium as chlorides. Bone-sample analyses for sodium and potassium have necessitated procedures such as wet or dry ashing, solution of the ash, precipitation of the calcium as carbonate, or oxalate with subsequent determination of Na or K in the supernatant by flame photometry, or by chemical gravimetric methods.

These authors have modified the method developed by G. B. Forbes and his group of separating cations in bone with quantitative recovery of sodium by column chromatography using Dowex 50 × 12, 50- to 100-mesh cation exchange resin. A small exchange column is described so that smaller bone samples can be tested than by the original Forbes method. Quantitative recovery of K as well as Na is made in separate fractions. Drying and ashing of bone is not necessary, an advantage when isotopes of Na and K are used. The authors did 300 examinations of bone biopsies and 6 experiments with synthetic mixtures by the method described. Radioactive Na and K were employed so that any contamination of the K fraction by Na could be detected. Recovery rates for Na and K in the same sample gave deviations of less than 3 per cent and 6 per cent, respectively, from the true content. When sodium and potassium were in separate samples there was less than 2 per cent and less than 7 per cent deviation, respectively, from the true content. With competent direction of a clinical biochemist a technician should be able to employ the method described by the authors. E. COHEN

Changes of Basal Metabolic Rate in Man in Semistarvation and Refeeding. F. Grande, J. T. Anderson, and A. Keys. *J. Appl. Physiol.* 12: 230, 1958.

Semistarvation diets of carbohydrates in the form of starch jelly bars provided diets of about 1,000 cal/day. Control diets provided 3,280–3,966 cal/day and recovery diets around 5,300 cal/day. During restriction vitamins and salt were supplied. Physical activity on a treadmill costing 1,200 cal was provided. Water was supplied from 900–1,800 cc/day or ad lib. The gross BMR was decreased in all cases of semistarvation. This fall in BMR was also observed if it was calculated per unit of gross weight, body surface, or per unit of "cells." This last was calculated as gross weight loss less fat, extracellular fluid, and bone minerals.

M. J. OPPENHEIMER

Effects of 5-Fluouracil on Human Bronchogenic Carcinoma Grown in Hamster Cheek Pouch. D. E. Wishnow and D. K. Sirota. *Proc. Soc. Exper. Biol. & Med.* 98: 770, 1958.

Fragments of the Skiff bronchogenic carcinoma were transplanted into the cheek pouch of male and female golden hamsters weighing 40 to 80 g. All animals were given 50 mg/kg cortisone subcutaneously every fourth day. From the fifth day after transplantation on 5-fluouracil dissolved in water was given either as a low dose of 25–30 mg/kg/day or as a high dose of 50–60 mg/kg/day for three or seven days. The effect of uracil on growth of the transplanted tumor as measured by weight was studied. The low dose was not significantly effective inasmuch as the tumors transplanted to control or to experimental animals had about the same weights. The high dose, however, caused considerable loss of weight and of the hamsters inhibited growth of the grafted tumors, their weights being reduced by almost four-fifths. Differences in the structure of the tumors of the treated and untreated series were not established.

M. SILBERBERG

Anorexia Nervosa: A Somatic Disorder. E. Williams. *Brit. M. J.* 2: 190, 1958.

Anorexia nervosa is reviewed in the light of experience of 49 females admitted to the London Hospital since 1897; there were two males not considered in this report. A number of the patients were followed up for long periods. Twenty-three of the 49 women recovered completely, but 10 died (8 "solely of malnutrition"), a higher death rate than is usually reported.

Any physician who may deal with this condition is advised to read this report; it cannot be adequately abstracted. The broad conclusion is that the purely nutritional aspect is probably the most important and the best results are obtained by tube feeding in the hospital. Specialized psychotherapy is not indicated, and it can be misleading to regard these patients as mentally ill; the circumstances which start the loss of appetite are often extraordinarily trivial. In rare cases leucotomy may be required.

F. E. HYTTEN

Metabolic and Nutritional Studies in Mice with a Hereditary Myopathy (Dystrophia Muscularis). N. Baker, M. Tubis, and W. H. Blahd. *Am. J. Physiol.* 193: 525, 1958.

Nutritional, chemical, and metabolic studies have been carried out on mice with hereditary muscular dystrophy and their littermate controls. Certain characteristics of the dystrophic syndrome which may not have been emphasized previously are described: denudation of the eyelids, periocular inflammation, tremors, and an unusual reflex involving the head and neck, inflammation of the penis, and diminished bone growth. The dystrophic mice consumed, on the average, more food per day per unit body weight than their normal controls. Parenteral administration of vitamins A, D, E, the B-complex vitamins, and ascorbic acid failed to reverse any of the dystrophic syndrome in eight dystrophic mice. The metabolic rate was normal (per unit weight basis) as measured by the rate of CO_2 production; similarly, acetate-I-C^{14} was oxidized to $C^{14}O_2$ at the same rate in normal and dystrophic mice. Finally, levels of plasma glucose, cholesterol, protein-bound I^{131}, and liver

cholesterol were not significantly different in a small group of normal and dystrophic mice. AUTHORS

Effect of Low Sodium Diet on Sodium Content and Radiosodium Exchange in Rat Bone. G. B. Forbes. *Proc. Soc. Exper. Biol. & Med.* 98: 153, 1958.

Twenty-day-old male albino rats of the Rochester strains were fed diet containing 0.011 per cent Na; pair-fed controls were kept on the same diet containing 0.55 per cent Na. Two and one-half to four hours before termination of the experiment, which was continued for four weeks, the animals received an intraperitoneal injection of 2.5 μc/100 g body weight of radiosodium.[22] Na, Cl, and H_2O content of serum and bones were determined and the specific activity of the crystal Na fraction was calculated. The rats fed the low-sodium diet failed to grow and their bones contained about 10 per cent less sodium than those of the controls. The exchange of radiosodium declined similarly with the consumption of the low Na diet. M. SILBERBERG

Electrolyte Metabolism in Pyridoxine, Riboflavin and Pantothenic Acid-Deficient Rats. E. J. Diamant and K. Guggenheim. *Am. J. Physiol.* 191: 108, 1957.

Muscle and plasma electrolyte concentrations were determined in rats suffering from pyridoxine, riboflavin, and pantothenic-acid deficiencies. Muscle of deficient rats contained more sodium and chloride than that of normal animals. There was also an increase in the plasma chloride content in pyridoxine and riboflavin-deficient rats. A decrease was observed in the potassium content of muscle in pyridoxine, and of the sodium level in plasma of riboflavin-deficient animals. Cortisone, when administered to pyridoxine-deficient animals, reduced muscle sodium and chloride, and increased its potassium concentration. No such effect is found when cortisone is injected into normal or adrenalectomized rats maintained on a full diet. A saline load was imposed on pyridoxine-deficient rats. They responded with a diminished excretion of water, sodium, and chloride. Cortisone, which under our experimental conditions had no effect upon the excretion of these substances in normal rats, increased, however, the excretion of water, sodium, and chloride when given to pyridoxine-deficient rats. The retention of sodium and chloride in our deficient rats and their increased excretion following treatment with cortisone is interpreted as a consequence either of the decreased glomerular filtration found in pyridoxine, riboflavin, and pantothenic-acid deficiencies, and/or the increased tubular reabsorption resulting from adrenal insufficiency, which both can be restored to normal again by administration of cortisone. AUTHORS

Influence of Dietary Sodium Chloride on Incidence of Urinary Calculi in Sheep. C. J. Elam, W. E. Ham, and B. H. Schneider. *Proc. Soc. Exper. Biol. & Med.* 95: 769, 1957.

In sheep, addition of potassium acid phosphate to the diet markedly increases the incidence of urinary calculi. Phosphorus and potassium are important in the etiology of these stones. The highest incidence of calculi was produced if both potassium and phosphorus were given. Crossbred wether lambs weighing about 84 lb were fed a stock diet supplemented with vitamins A and D in order to eliminate the possible influence of a low vitamin level in the formation of stones. Variables in the diet were K_2HPO_4, NaCl, beet pulp, and beet pulp ash. The diets were fed for 105 days. No stones were found in the sheep receiving NaCl. However, most urinary calculi developed in those animals that had received supplements of potassium acid phosphate. Beet pulp and beet pulp ash had no effect on the formation of urinary stones. M. SILBERBERG